From: Signal Investigation Coordinator
To: s22
Subject: FW: NEXIUM esomeprazole - Safety Signal Notification [SEC=OFFICIAL]
Date: Wednesday, 16 December 2020 2:02:07 PM
Attachments: image001.png
signal-notification-esomeprazole-nephrotoxicity_1.pdf

Hi s22,

FYI. I could not find any relevant issues in the database.

Regards,

s22

s22
Signal Investigation Coordinator

Medicines Regulation Division | Health Products Regulation Group
Pharmacovigilance and Special Access Branch
Australian Government Department of Health
E: s22@health.gov.au
E: si.coordinator@health.gov.au
Location: Therapeutic Goods Administration GD 59
PO Box 100, Woden ACT 2606, Australia
Phone: 6289 3574
The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: s22@astrazeneca.com>
Sent: Tuesday, 15 December 2020 11:15 AM
To: Signal Investigation Coordinator <si.coordinator@health.gov.au>
Cc: s22@astrazeneca.com>; s22
s22@astrazeneca.com>; s22@astrazeneca.com>
Subject: RE: NEXIUM esomeprazole - Safety Signal Notification

Dear TGA Signal Investigation Coordinator,

This is an update to the safety signal notification, which AstraZeneca sent through previously on 15 Oct for 'nephrotoxicity'

in relation to the following products:

ARTG	Product Name
74133	NEXIUM esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
74134	NEXIUM esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
75726	NEXIUM esomeprazole (as magnesium trihydrate) 20 mg tablet bottle
75727	NEXIUM esomeprazole (as magnesium trihydrate) 40 mg tablet bottle
96678	NEXIUM IV esomeprazole (as sodium) 40 mg powder for injection vial
135726	NEXIUM esomeprazole (as magnesium trihydrate) 10 mg enteric coated granules for oral suspension sachet
202457	AXAGON esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
202458	AXAGON esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
202463	REFEXXIN esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
202464	REFEXXIN esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
281690	NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack

Please find attached, the follow up safety signal notification summarizing the investigation.

Based on the outcome of the investigation AstraZeneca considers the safety signal refuted and closed.

Should you require any further information regarding this safety signal, please do not hesitate to contact me directly via
the details provided below.

Kind Regards,

s22 [redacted]
Regulatory Affairs Associate

AstraZeneca
66 Talavera Road, Macquarie Park, NSW 2113, Australia
s22 [redacted]

From: s22 [redacted] @astrazeneca.com>
Sent: den 15 oktober 2020 20:38
To: si.coordinator@health.gov.au
Cc: s22 [redacted] @astrazeneca.com>; s22 [redacted] s22 [redacted] @astrazeneca.com>; s22 [redacted] @astrazeneca.com>
Subject: NEXIUM esomeprazole - Safety Signal Notification

Dear Signal Investigation Coordinator,

AstraZeneca hereby notifies the TGA of a safety signal regarding nephrotoxicity in relation to the following products:

ARTG	Product Name
74133	NEXIUM esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
74134	NEXIUM esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
75726	NEXIUM esomeprazole (as magnesium trihydrate) 20 mg tablet bottle
75727	NEXIUM esomeprazole (as magnesium trihydrate) 40 mg tablet bottle
96678	NEXIUM IV esomeprazole (as sodium) 40 mg powder for injection vial
135726	NEXIUM esomeprazole (as magnesium trihydrate) 10 mg enteric coated granules for oral suspension sachet
202457	AXAGON esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
202458	AXAGON esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
202463	REFEXXIN esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
202464	REFEXXIN esomeprazole (as magnesium trihydrate) 40 mg tablet blister pack
281690	NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack

Please find attached a safety signal notification summarising the current status of the assessment.

AstraZeneca is currently evaluating this safety signal and will provide an update once the assessment is complete.

Please note that AXAGON and REFEXXIN are additional trade name products for the parent product NEXIUM, but are not currently marketed.

Should you require any further information regarding this safety signal notification, please do not hesitate to contact me.

Kind regards,

s22 [redacted]
Senior Regulatory Affairs Associate

AstraZeneca
66 Talavera Road, Macquarie Park, NSW 2113, Australia
s22 [redacted]
[redacted] astrazeneca.com

Safety Signal Notification	
Drug Substance	Esomeprazole
Date	03 December 2020

Safety Signal Notification for NEXIUM™ (Esomeprazole) and Nephrotoxicity

TABLE OF CONTENTS

1 PRODUCT OVERVIEW

Date of this notification	03 December 2020
Active substance(s) (invented name(s))	Esomeprazole
Pharmaceutical form(s)/Route(s) of administration / Strength(s)	NEXIUM™ tablets 20 mg and 40 mg; granules for oral suspension 10 mg; IV 40 mg Route of administration – Oral; Intravenous
Marketing authorisation holder	AstraZeneca
International Birth Date	10 March 2000
QPPV	s22 [redacted] (Patient Safety Manger)
MAH contact person for the signal	s22 [redacted] (Regulatory Affairs Associate)
Status of Signal Evaluation	Rejected

2 SIGNAL DESCRIPTION

2.1 SIGNAL OVERVIEW

The safety topic of nephrotoxicity with NEXIUM use has been identified as a signal for review.

2.2 SIGNAL TRIGGER AND VALIDATION OVERVIEW

Signal Trigger

A safety signal observation was made on 16 September 2020, the sources are marked below.

- ☐ Literature
- ☐ Clinical trials
- ☐ Statistical Analysis (Internal & External Database)
- ☐ Other
- ☐ MAH Safety database (Case Series)
- ☒ Regulatory Authority [US FDA]
- ☐ Pre-Clinical Data

Signal Evaluation Source(s)

The safety signal evaluation was completed on 06 October 2020. The sources used to further evaluate are marked below.

- ☒ Literature
- ☒ Clinical trials
- ☒ Statistical Analysis (Internal &External Database)
- ☒ Other: Pre-clinical
- ☒ MAH Safety database (Case Series)
- ☒ Epidemiology
- ☐ Regulatory Authority [provide name below]

2.3 SIGNAL ASSESSMENT

An assessment was made using several sources of data.

A search and review of sources highlighted above is summarized as below:

From the cases identified in AstraZeneca global safety database for NEXIUM, a total of 6 case reports were considered for further evaluation. These cases reported biopsy-proven acute interstitial nephritis, and the patients presented with non-specific signs and symptoms like vomiting, generalize malaise, anorexia, weight loss, cough, loin pain etc associated with ARF rather than extrarenal symptoms of fever, rash, arthralgia which are typical of hypersensitivity reaction.

The review of the cases did not identify any asymptomatic acute decline in the renal function.

There were no noteworthy case reports pertaining to CKD as distinct medical entity.

A review of pre-clinical data was performed and it was found that the kidney was not seen as a target organ for toxicity in any of the several toxicology studies conducted with esomeprazole.

From a review of clinical trial data, there was no pattern of imbalance identified with regard to renal events or events related to kidney function for esomeprazole versus comparators.

A review of literature was performed and the reviewed publications did not provide new information and do not support use of the term “asymptomatic” when describing acute decline in renal function. Further, it is AstraZeneca’s view that the reviewed publications do not support an increased risk of Chronic kidney disease with PPI use.

3 COMPANY POSITION

Based on this assessment, it is the opinion of AstraZeneca that none of the reviewed data support either (a) an asymptomatic acute decline in renal function, or (b) an increased risk of chronic inflammation or chronic decline in renal function with PPI use.

At the time of preparing this document, AstraZeneca considers the signal refuted and closed and no update to the Core Data Sheets (CDSs) is warranted.

From: s22
To: s22
Subject: New issue for discussion please [SEC=OFFICIAL]
Date: Thursday, 25 June 2020 2:53:54 PM
Attachments: image001.png

Hi s22

Could you please add this one to the agenda next week 'FOR DISCUSSION' .

Thanks!

s22

Issue # – Proton pump inhibitors and increased risk of tubulointerstitial nephritis – Unallocated (Discussant s22 – TRIM container
Issue source: Environmental scanning – FDA
Issue summary: FDA is requesting all PPI medicine to amend the current USPI Warnings and Precautions and Adverse Reactions section, and other relevant sections, to change the term in the currently approved USPI from "acute interstitial nephritis" to "tubulointerstitial nephritis", and to add additional content to the Warnings and Precautions section FDA has become aware of an **increased risk of subclinical acute or chronic interstitial nephritis** associated with PPIs **leading to chronic renal inflammation and reduced renal function** reported in published literature. All sponsors are required to submit annotated product information or rebuttal within 30 days. FDA plans to approve all amendments on the same day - stated to be 15 September 2020. Requested FDA proposed wording and literature references prompting this action (if known). AEMS – 177 reports of 'tubulointerstitial nephritis' out of 401 Renal SOC reports. (Search: Rabeprazole, Pantoprazole, Esomeprazole, Omeprazole, Lansoprazole)
Rationale for action and priority: Await reply from sponsor. Medium.
Additional background information:
Action and priority:

s22

s22 – Signal Investigation Unit

s22

Medicines Regulation Division | Health Products Regulation Group
Pharmacovigilance and Special Access Branch
Australian Government Department of Health
T: s22 | E: s22 @health.gov.au
Location: 136 Narrabundah Lane, SYMONSTON ACT 2609
PO Box 100, Woden ACT 2606, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: s22
To: Signal Investigation Coordinator
Cc: s22
Subject: RE: NEXIUM - Action Notification - Acute Tubulointerstitial Nephritis
Date: Friday, 8 December 2023 3:53:08 PM
Attachments: action-notification-esomeprazole-tin-sahpra.pdf

Dear Signal Investigation Coordinator,

Please find attached the action notification document which provides further details in relation to the actions taken by SAHPRA, along with AstraZeneca's position on these actions.

Regards,
s22

From: s22
Sent: Friday, 8 December 2023 3:32 PM
To: 'Signal Investigation Coordinator' <si.coordinator@health.gov.au>
Cc: s22 @astrazeneca.com>; s22 @astrazeneca.com>
Subject: NEXIUM - Action Notification - Acute Tubulointerstitial Nephritis

Dear Signal Investigation Coordinator,

AstraZeneca hereby notifies the TGA of actions taken by the South African Health Products Regulatory Authority (SAHPRA) for NEXIUM that have resulted in a label imposition regarding acute tubulointerstitial nephritis with proton pump inhibitor (PPI) use.

This action notification is associated with the following esomeprazole products:

Product	AUST R
NEXIUM esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack	74133
NEXIUM esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack	74134
NEXIUM IV esomeprazole 40 mg (as sodium) powder for injection vial	96678
NEXIUM esomeprazole 10 mg (as magnesium trihydrate) enteric coated granules for oral suspension sachet	135726
AXAGON esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack	202457
AXAGON esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack	202458
REFEXXIN esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack	202463
REFEXXIN esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack	202464
NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack	281690
ESOPREZE esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack	349670
ESOPREZE esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack	349671

On 16 January 2023, AstraZeneca received a letter from SAHPRA with recommendations to update the South Africa Professional Information/Patient Information Leaflet and issue a Dear Healthcare Professional Letter with wording in line with the United States FDA recommendations, pertaining to the topic of acute tubulointerstitial nephritis with PPI use.

On 23 January 2023, AstraZeneca accepted the SAHPRA recommendations as a regulatory imposition. There is no change to the company position in relation to this topic.

Please note that AXAGON (AUST R 202457, 202458) and REFEXXIN (AUST R 202463, 202464) are not currently marketed in Australia.

Should you require any further information, please do not hesitate to me.

Regards,

s22
Regulatory Affairs Manager

AstraZeneca
s22
astrazeneca.com

Action Notification	
Drug Substance	Esomeprazole
Date	07 December 2023

Action Notification for NEXIUM® (esomeprazole) and Dear Health Care Professional Letter (DHCPL) & Professional Information (PI)/Patient Information Leaflet (PIL) update imposition regarding tubulointerstitial nephritis (TIN) by South African Health Products Regulatory Authority (SAHPRA)

TABLE OF CONTENTS

1 PRODUCT OVERVIEW

Date of this notification	07 December 2023
Active substance(s) (invented name(s))	Esomeprazole
Pharmaceutical form(s)/Route(s) of administration / Strength(s)	NEXIUM®: capsules/ tablets 20 mg and 40 mg; granules for oral suspension 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg; infusion/injection 40 mg Route of administration – Oral; Intravenous
International Birth Date	10 March 2000
Health Authority Requesting the Action	South African Health Products Regulatory Authority (SAHPRA)
Action Taken by Health Authority	1. Local Label Imposition: Request for addition to local label not reflected in CDS (additions to 'Side effect, 'Post-marketing exposure and 'Warnings and Precautions' sections of the PI/PIL). 2. Safety Communication: DHCP communication required regarding the risk of acute TIN associated with PPIs.

2 ACTION DESCRIPTION

2.1 ACTION OVERVIEW

AstraZeneca received a letter dated 15 December 2020 from South African Health Products Regulatory Authority (SAHPRA) with recommendations to update South Africa Professional Information (PI)/Patient Information Leaflet (PIL) and issue a Dear Health Care Professional Letter (DHCPL), pertaining to the topic of acute Tubulointerstitial nephritis (TIN) with proton pump inhibitor (PPI) use.

Based on the comprehensive medical & scientific review of the topic of TIN associated with the PPI use, AstraZeneca had responded that it is AstraZeneca's view that a label change was not warranted and, consequently, a DHCPL was not required.

On 16 January 2023, AstraZeneca received a letter from SAHPRA with recommendations to update South Africa PI/PIL and issue a DHCPL with wording in line with the United States Food and Drug Administration (US FDA) recommendations, pertaining to the topic of acute TIN with PPI use. SAHPRA recommended as below:

- *"Applicants of PPI containing medicines update PI/PIL of their products in line with the US FDA recommendations. Applicants should consider the following:*

  - *Treatment with PPIs must be stopped when interstitial nephritis is suspected,*
  - *Contraindication of PPI use in patients who previously experienced interstitial nephritis while on treatment with PPI.*
  - *Use of the term acute tubulointerstitial nephritis in keeping with the current terminology by MedDRA.*
- *Applicants distribute a DHCPL to alert healthcare professionals of the risk of tubulointerstitial nephritis associated with PPIs."*

The DHCPL was to update on the safety information regarding acute TIN that has been observed with the use of PPIs.

On 23 January 2023, AstraZeneca submitted the DHCPL for NEXIUM/AXIAGO (esomeprazole) for SAHPRA's approval. On 15 February 2023, SAHPRA requested for a joint DHCPL in collaboration with two other innovator companies (Takeda and Janssen), with Takeda leading the activity. On 23 February 2023, AstraZeneca sent the reviewed joint DHCPL for NEXIUM/AXIAGO to Takeda for SAHPRA's submission. The joint DHCPL was submitted by Takeda to SAHPRA on 25 April 2023. Between 25 April 2023 and 01 November 2023, there were multiple communications between the three innovator companies and SAHPRA on the text to be included in the DHCPL.

On 10 November 2023, SAHPRA approved the joint DHCPL.

2.2 COMPANY POSITION

In response to this specified action, AstraZeneca's position was that there is insufficient evidence and that a label change was not warranted and, consequently, a DHCPL was not required. However, AstraZeneca acknowledge the SAHPRA's position and accepted the SAHPRA recommendations as a regulatory imposition and will implement the action as requested.

3 COMPANY ACTION

Following discussions with the requesting Health Authority,

1. AstraZeneca has taken the following action: The joint DHCPL, titled "The risk of acute tubulointerstitial nephritis (TIN) associated with proton pump inhibitors (PPIs)" was disseminated in South Africa by our partner on 24 November 2023.

The following text was included as Advice to healthcare professionals:

- Treatment with Nexium®/Axiago® must be stopped when TIN is suspected.

- Nexium® / Axiago® are contraindicated in patients who previously experienced TIN while on treatment with PPIs.
- Patients should be asked to report any decrease in urine volumes or if they suspect that there is blood in their urine while on PPIs.

2. AstraZeneca will take the following action: The South Africa PI and PIL will be updated by including the SAHPRA recommended text in 'Side effect, 'Post-marketing exposure and 'Warnings and Precautions' sections of the PI/PIL.

From: s22
To: eSubmissions
Cc: s22
Subject: e006250; sequence 0017 - LOSEC ACIMAX OMEPRAL omeprazole - 9D(2) Safety Related Request, 9D(3) MEC to the product information
Date: Thursday, 27 April 2023 6:15:29 PM
Attachments: image001.png
e006250.zip

Dear TGA,

RE: Safety Related Request not requiring the submission of data for evaluation under s.9D(2) 9D(3) Minor editorial changes to the product information

LOSEC omeprazole (as magnesium) 10mg, 20mg, tablet blister pack - AUST R 63414, 63416
ACIMAX omeprazole (as magnesium) 20mg tablet blister pack – AUST R 67306
OMEPRAL omeprazole (as magnesium) 20mg tablet blister pack –AUST R 120594
eIdentifier: e006250 Sequence: 0017
Related sequence: 0017

On behalf of the sponsor Pharmaco Australia Ltd (client ID 45504), please find attached the eCTD sequence for above-mentioned 9D(2) Safety Related Request and 9D(3) Minor editorial changes to the product information.

Please feel free to contact me if you have any questions regarding the above submission.

Thank you.
Kind regards,

s22

s22
s47G

s47G

s22

s22 s47G

s22
s47G

Pharmaco
Always from the heart

26 April 2023

Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Re: Safety Related Request not requiring the submission of data for evaluation under s.9D(2) 9D(3) Minor editorial changes to the product information

LOSEC omeprazole (as magnesium) 10mg, 20mg, tablet blister pack - AUST R 63414, 63416
ACIMAX omeprazole (as magnesium) 20mg tablet blister pack – AUST R 67306
OMEPRAL omeprazole (as magnesium) 20mg tablet blister pack – AUST R 120594
eIdentifer: e006250 Sequence: 0017
Related sequence: 0017

Dear Madam/Sir,

PION: PI - make safety related changes no data

Pharmaco Australia Ltd (client ID 45504) herewith submits a Safety Related Request (no data) under section 9D(2) of the Therapeutic Goods Act 1989 for the above mentioned product(s). The Consumer Medicine Information (CMI) has been amended accordingly to align with the changes made to the PI. The sponsor provide the assurance that no other changes have been made to the PI and ARTG other than the changes specifically mentioned in this request.

The following documents are provided:
• A clean and marked-up (annotated) copy of the draft revised PI for Losec, Acimax and Omepral
• A clean and marked-up (annotated) copy of the draft revised CMI for Losec, Acimax and Omepral
• Justification for the proposed variation

Details of the safety-related request:

Section Changed	**Summary of new information**
PI	
4.4 Special Warnings And Precautions For Use	Renal impairment Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure. Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.
4.8 Adverse Effects	Renal and urinary disorders Rare: Tubulointerstitial nephritis (with possible progression to renal failure)

(Undesirable Effects)	
Section Changed	**Summary of new information**
CMI	
6. Are there any side effects?	When taking ACIMAX®/ LOSEC®/ OMEPRAL®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

PIME: PI - make minor editorial changes

The sponsor would like to make minor editorial changes to format and grammatical errors in the PI.

The following documents are provided:

- A clean and marked-up (annotated) copy of the draft revised PI for Losec, Acimax and Omepral

Electronic submission information

Technical validation of the eCTD submission was conducted using LORENZ eValidator v22.2 and the sequence meets all validation criteria. This sequence is provided as a zip file (approx. size < 10 MB) via email. The file has been scanned with antivirus software (Trend Micro Security Agent) and is free of known viruses.

For any questions regarding this submission, including regulatory and technical aspects, please contact s22 by email at s22 s47G.

Yours sincerely,

s22
s22
s47G
s22

CHEPLAPHARM

To Whom It May Concern

13/04/2023

Justification statement for implementation a new safety signal for omeprazole-containing products

Dear Sir or Madam,

we, CHEPLAPHARM Arzneimittel GmbH, submitted the periodic safety update report (PSUR) to the European authorities for the medicinal products containing omeprazole. The evaluation procedure on EU level started on 04 August 2022 and the recommendation was adopted by the PRAC on 01 December 2022.

Taking into account the PRAC Assessment Report on the PSUR for omeprazole, the scientific conclusions are as follows:
In view of available data on nephrotoxicity from the literature and spontaneous reports, the EU considers a causal relationship between omeprazole and tubulointerstitial nephritis (with possible progression to renal failure) is at least a reasonable possibility. The product information of products containing omeprazole should be amended accordingly.

To guarantee the patient safety, CHEPLAPHARM Arzneimittel GmbH as global owner of the product would like to implement this safety signal also for the omeprazole containing products registered in Australia, namely Losec, Acimax and Omepral, in alignment with the local MAH Pharmaco (Australia) Ltd.

The warning was included in PI section 4.4, in section 4.8 with rare frequency and in CMI section 6. The relevant product information is included within the variation application.

Yours sincerely,

s22

s22
Manager Regulatory Affairs
CHEPLAPHARM Arzneimittel GmbH

ADDRESS
CHEPLAPHARM ARZNEIMITTEL GMBH
Ziegelhof 24 _ 17489 Greifswald_Germany

CONTACT
T. +49 3834 3914-0 _ F. +49 3834 3914-119
info@cheplapharm.com _ cheplapharm.com

s22

BANK DETAILS
ING Bank _ IBAN: DE73 5002 1000 0018 1127 06 _ SWIFT-Code: INGBDEFFXXX
UniCredit Bank - Hypovereinsbank _ IBAN: DE44 2003 0000 0616 2047 31 _ SWIFT-Code: HYVEDEMM300

REGISTERING COURT
Stralsund _ HRB 5896

Module 1.0.2 Lifecycle Management Tracking Table – e006250

Sequence	Sequence Type	Sequence Description	Related Sequence
0012	H - Minor Variation, Not Resulting in a New Register Entry	Initial	0012
0013	H - Minor Variation, Not Resulting in a New Register Entry	Initial	0013
0014	Supplementary Information	Response to request for information – 2022-10-13	0013
0015	9D(2) Safety related request not requiring the evaluation of data	Initial	0015
0016	Supplementary Information	Product Information	0015
0017	9D(2) Safety related request not requiring the evaluation of data and 9D(3) - Change to PI	Initial	0017

Preceding sequences have been reviewed under e001857 prior to partial transfer from the original sponsor.

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Application ID: PM-2023-MV-02304-1
Date: 12-Apr-2023
Status: Passed validation
Applicant Reference: Omeprazole SRR not requiring the submission of data for evaluation + MEC
eSubmission Id: e006250

Applicant Information

Applicant:	s47G [redacted]
Contact:	s22 [redacted]
Phone number:	s22 [redacted]
Email:	s22 s47G [redacted]
Sponsor:	Pharmaco Australia Ltd
Is the sponsor responsible for all invoices regarding this submission:	Yes
Billing address (Sponsor):	Locked Bag 1009 GORDON NSW AU
Regulatory correspondence address:	s47G [redacted]

Fee Item: 2A(a), Legislative Basis: 9D(3)

Group:	Product Information (PI)
Category:	Minor Editorial Changes
Type:	PIME: PI - Make minor editorial changes
Assurances:	A clean and marked-up copy of the draft revised PI is provided. Assurance is given that the only changes being requested are those identified in this request. Details of the changes are provided and they meet the definition of minor editorial changes. Relevant justification and evidence is provided.
Legislative Basis:	9D(3)
Comment:	
Selected ARTG IDs:	63414, 63416, 67306, 120594

Fee Item: 2A(a), Legislative Basis: 9D(2)

Group:	Product Information (PI)
Category:	Safety Related Request not requiring the submission of data for evaluation
Type:	PION: PI - Make safety related changes no data
Assurances:	A clean and marked-up copy of the draft revised PI is provided. A justification for the proposed variation is provided. Assurance is given that the only changes being requested are those identified in this request. Details of the safety-related request are provided. No evaluation of data is required for this request.
Legislative Basis:	9D(2)
Comment:	
Selected ARTG IDs:	63414, 63416, 67306, 120594

Supporting Information

Fee(s)

Variation group	Legislative basis	Fee Item	Fee $	Will a new ARTG Id be generated as a result of this submission?

Product Information (PI)	9D(2),9D(3)	2A(a)	$1806	No

Warning Message(s)

Unknown is an invalid container closure. It is being used in the following goods: 120594, 63414, 63416, 67306. Please update data within 'Container and Shelf Life' when you are next submitting a variation affecting that section.

Container material is required for the following goods: 67306. Please update data within 'Container and Shelf Life' when you are next submitting a variation affecting that section.

Document generated **12/04/2023 18:50 PM**

AUSTRALIAN PRODUCT INFORMATION
ACIMAX® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ACIMAX Tablets is omeprazole magnesium, a substituted benzimidazole. ACIMAX is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ACIMAX Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the ACIMAX logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACIMAX Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACIMAX Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: ACIMAX Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with ACIMAX Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, ACIMAX Tablets 10 mg once daily. If needed, this dose should be increased to ACIMAX Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is ACIMAX Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is ACIMAX Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: ACIMAX Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	ACIMAX Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	ACIMAX Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of ACIMAX Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ACIMAX. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when ACIMAX Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ACIMAX Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ACIMAX is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of ACIMAX Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ACIMAX tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ACIMAX is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

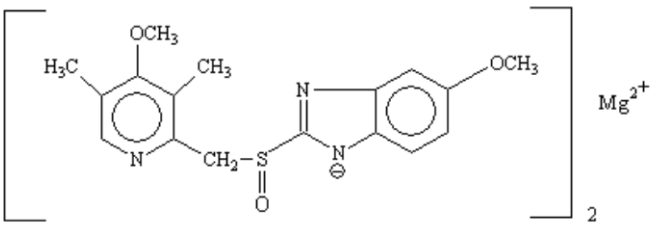
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

18 August 1999

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
LOSEC® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg and 20 mg tablets containing omeprazole magnesium 10.3 mg and 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

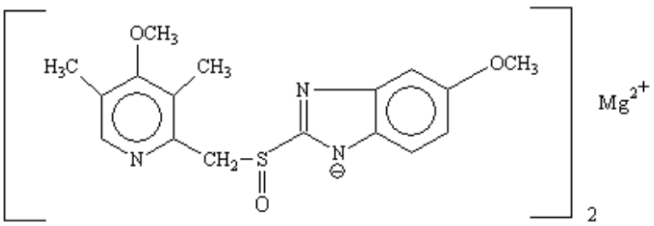
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
OMEPRAL® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in OMEPRAL Tablets is omeprazole magnesium, a substituted benzimidazole. OMEPRAL is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

OMEPRAL Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the OMEPRAL logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OMEPRAL Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

OMEPRAL Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: OMEPRAL Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with OMEPRAL Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, OMEPRAL Tablets 10 mg once daily. If needed, this dose should be increased to OMEPRAL Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is OMEPRAL Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is OMEPRAL Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: OMEPRAL Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	OMEPRAL Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	OMEPRAL Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of OMEPRAL Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping OMEPRAL. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g.

diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when OMEPRAL Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant

treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OMEPRAL Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OMEPRAL is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is

dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of OMEPRAL Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests

were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical reSection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OMEPRAL tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate,

sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

OMEPRAL is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

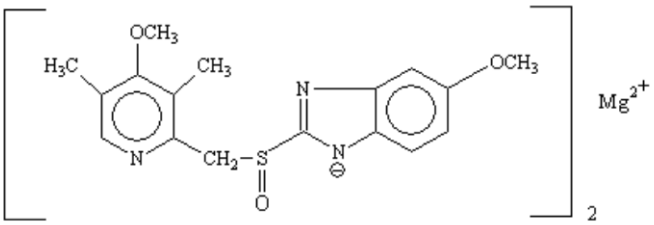
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue
Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

1 November 2005

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
ACIMAX® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ACIMAX Tablets is omeprazole magnesium, a substituted benzimidazole. ACIMAX is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ACIMAX Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the ACIMAX logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACIMAX Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACIMAX Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: ACIMAX Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with ACIMAX Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, ACIMAX Tablets 10 mg once daily. If needed, this dose should be increased to ACIMAX Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is ACIMAX Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is ACIMAX Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: ACIMAX Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	ACIMAX Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	ACIMAX Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of ACIMAX Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ACIMAX. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when ACIMAX Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ACIMAX Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ACIMAX is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs

within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of ACIMAX Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was~~ere~~ markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ACIMAX tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ACIMAX is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

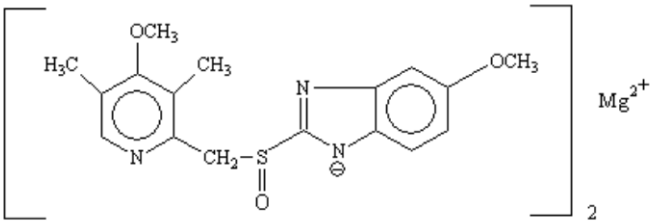
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

18 August 1999

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
LOSEC® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg and 20 mg tablets containing omeprazole magnesium 10.3 mg and 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs

within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was~~ere~~ markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

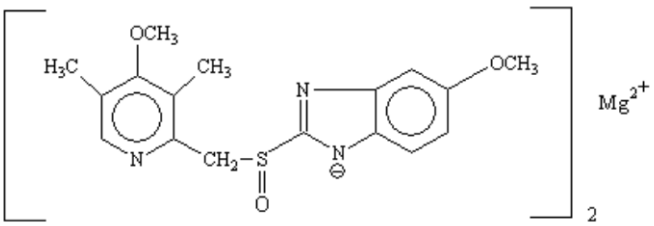
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
OMEPRAL® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in OMEPRAL Tablets is omeprazole magnesium, a substituted benzimidazole. OMEPRAL is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

OMEPRAL Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the OMEPRAL logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OMEPRAL Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

OMEPRAL Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: OMEPRAL Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with OMEPRAL Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, OMEPRAL Tablets 10 mg once daily. If needed, this dose should be increased to OMEPRAL Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is OMEPRAL Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is OMEPRAL Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: OMEPRAL Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	OMEPRAL Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	OMEPRAL Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of OMEPRAL Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping OMEPRAL. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g.

diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when OMEPRAL Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant

treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OMEPRAL Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OMEPRAL is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is

dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of OMEPRAL Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests

were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two--year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects wasere markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical reSection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OMEPRAL tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate,

sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

OMEPRAL is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

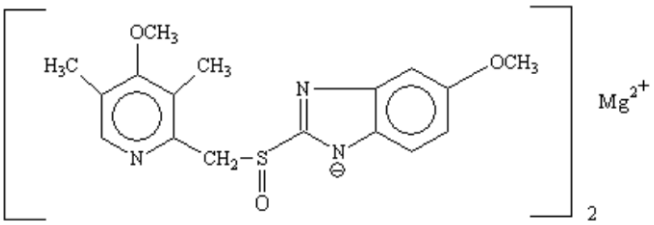
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

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Level 13, 465 Victoria Avenue
Chatswood NSW 2067
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Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

1 November 2005

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

ACIMAX®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking ACIMAX®?

ACIMAX® contains the active ingredient omeprazole (as magnesium). ACIMAX® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using ACIMAX®? in the full CMI.

2. What should I know before I take ACIMAX®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use ACIMAX®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with ACIMAX® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take ACIMAX®?

- Take one ACIMAX® tablet each day, unless your doctor has told you otherwise.
- Swallow ACIMAX® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use ACIMAX®?

More instructions can be found in Section 4. How do I use ACIMAX®? in the full CMI.

5. What should I know while using ACIMAX®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using ACIMAX®. • Tell your doctor if you become pregnant while you are taking ACIMAX®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take ACIMAX® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how ACIMAX® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your ACIMAX® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using ACIMAX®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

ACIMAX®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using ACIMAX®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using ACIMAX®.**

Where to find information in this leaflet:

1. Why am I taking ACIMAX®?

ACIMAX® contains the active ingredient omeprazole (as magnesium). ACIMAX® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

ACIMAX® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

ACIMAX® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

ACIMAX® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

ACIMAX® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

ACIMAX® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When ACIMAX® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

ACIMAX® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

ACIMAX® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

ACIMAX® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that ACIMAX® is addictive.

2. What should I know before I take ACIMAX®?

Warnings

Do not take ACIMAX® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by ACIMAX®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to ACIMAX® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take ACIMAX® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take ACIMAX® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in ACIMAX® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take ACIMAX® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with ACIMAX® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by ACIMAX® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take ACIMAX®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect ACIMAX®.

4. How do I take ACIMAX®?

How much to take

- Take one ACIMAX® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of ACIMAX® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of ACIMAX® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use ACIMAX® until your doctor tells you to stop.

When to take ACIMAX®

- Take ACIMAX® at about the same time each day.
- Keeping a regular time for taking ACIMAX® will help to remind you to take it.
- ACIMAX® can be taken with food or on an empty stomach.

How to take ACIMAX®

- Swallow ACIMAX® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking ACIMAX® for as long as your doctor recommends.
  In most patients, ACIMAX® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking ACIMAX® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use ACIMAX®

ACIMAX® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much ACIMAX®

If you think that you have used too much ACIMAX®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using ACIMAX®?

Things you should do

Take ACIMAX® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking ACIMAX®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking ACIMAX®.

Tell your doctor if you become pregnant while you are taking ACIMAX®.

Tell your doctor if your symptoms return.

Although ACIMAX® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking ACIMAX®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using ACIMAX®.

Things you should not do

- Do not take ACIMAX® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how ACIMAX® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your ACIMAX® in the blister pack until it is time to take them.
  If you take ACIMAX® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking ACIMAX® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with ACIMAX® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, ACIMAX® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking ACIMAX®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking ACIMAX®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What ACIMAX® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

ACIMAX® tablets do not contain gluten.

What ACIMAX® looks like

ACIMAX® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

ACIMAX® 20 mg (blister pack) - AUST R 67306

Who distributes ACIMAX®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

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This leaflet was prepared in April 2023.

LOSEC®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking LOSEC®?

LOSEC® contains the active ingredient omeprazole (as magnesium). LOSEC® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using LOSEC®? in the full CMI.

2. What should I know before I take LOSEC®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use LOSEC®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with LOSEC® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take LOSEC®?

- Take one LOSEC® tablet each day, unless your doctor has told you otherwise.
- Swallow LOSEC® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use LOSEC®?

More instructions can be found in Section 4. How do I use LOSEC®? in the full CMI.

5. What should I know while using LOSEC®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using LOSEC®. • Tell your doctor if you become pregnant while you are taking LOSEC®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take LOSEC® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how LOSEC® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your LOSEC® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using LOSEC®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

LOSEC®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using LOSEC®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using LOSEC®.**

Where to find information in this leaflet:

1. Why am I taking LOSEC®?

LOSEC® contains the active ingredient omeprazole (as magnesium). LOSEC® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

LOSEC® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

LOSEC® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

LOSEC® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

LOSEC® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

LOSEC® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When LOSEC® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

LOSEC® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

LOSEC® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

LOSEC® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that LOSEC® is addictive.

2. What should I know before I take LOSEC®?

Warnings

Do not take LOSEC® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by LOSEC®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to LOSEC® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take LOSEC® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take LOSEC® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in LOSEC® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take LOSEC® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with LOSEC® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by LOSEC® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take LOSEC®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect LOSEC®.

4. How do I take LOSEC®?

How much to take

- Take one LOSEC® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of LOSEC® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of LOSEC® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use LOSEC® until your doctor tells you to stop.

When to take LOSEC®

- Take LOSEC® at about the same time each day.
- Keeping a regular time for taking LOSEC® will help to remind you to take it.
- LOSEC® can be taken with food or on an empty stomach.

How to take LOSEC®

- Swallow LOSEC® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking LOSEC® for as long as your doctor recommends.
  In most patients, LOSEC® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking LOSEC® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use LOSEC®

LOSEC® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon

as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much LOSEC®

If you think that you have used too much LOSEC®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using LOSEC®?

Things you should do

Take LOSEC® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking LOSEC®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking LOSEC®.

Tell your doctor if you become pregnant while you are taking LOSEC®.

Tell your doctor if your symptoms return.

Although LOSEC® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking LOSEC®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using LOSEC®.

Things you should not do

- Do not take LOSEC® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how LOSEC® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your LOSEC® in the blister pack until it is time to take them.
  If you take LOSEC® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking LOSEC® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with LOSEC® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, LOSEC® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking LOSEC®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking LOSEC®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What LOSEC® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

LOSEC® tablets do not contain gluten.

What LOSEC® looks like

LOSEC® 10 mg tablets are light pink, oblong shaped, marked with 10 mg on one side and a logo on the other side.

LOSEC® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

LOSEC® 10 mg (blister pack) - AUST R 63414

LOSEC® 20 mg (blister pack) - AUST R 63416

Who distributes LOSEC®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany.

This leaflet was prepared in April 2023.

OMEPRAL®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking OMEPRAL®?

OMEPRAL® contains the active ingredient omeprazole (as magnesium). OMEPRAL® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using OMEPRAL®? in the full CMI.

2. What should I know before I take OMEPRAL®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use OMEPRAL®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with OMEPRAL® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take OMEPRAL®?

- Take one OMEPRAL® tablet each day, unless your doctor has told you otherwise.
- Swallow OMEPRAL® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use OMEPRAL®?

More instructions can be found in Section 4. How do I use OMEPRAL®? in the full CMI.

5. What should I know while using OMEPRAL®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using OMEPRAL®. • Tell your doctor if you become pregnant while you are taking OMEPRAL®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take OMEPRAL® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how OMEPRAL® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your OMEPRAL® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using OMEPRAL®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

OMEPRAL®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using OMEPRAL®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using OMEPRAL®.**

Where to find information in this leaflet:

1. Why am I taking OMEPRAL®?

OMEPRAL® contains the active ingredient omeprazole (as magnesium). OMEPRAL® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

OMEPRAL® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

OMEPRAL® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

OMEPRAL® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

OMEPRAL® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

OMEPRAL® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When OMEPRAL® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

OMEPRAL® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

OMEPRAL® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

OMEPRAL® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that OMEPRAL® is addictive.

2. What should I know before I take OMEPRAL®?

Warnings

Do not take OMEPRAL® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by OMEPRAL®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to OMEPRAL® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take OMEPRAL® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take OMEPRAL® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in OMEPRAL® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take OMEPRAL® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with OMEPRAL® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by OMEPRAL® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take OMEPRAL®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect OMEPRAL®.

4. How do I take OMEPRAL®?

How much to take

- Take one OMEPRAL® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of OMEPRAL® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of OMEPRAL® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use OMEPRAL® until your doctor tells you to stop.

When to take OMEPRAL®

- Take OMEPRAL® at about the same time each day.
- Keeping a regular time for taking OMEPRAL® will help to remind you to take it.
- OMEPRAL® can be taken with food or on an empty stomach.

How to take OMEPRAL®

- Swallow OMEPRAL® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking OMEPRAL® for as long as your doctor recommends.
  In most patients, OMEPRAL® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking OMEPRAL® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use OMEPRAL®

OMEPRAL® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much OMEPRAL®

If you think that you have used too much OMEPRAL®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using OMEPRAL®?

Things you should do

Take OMEPRAL® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking OMEPRAL®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking OMEPRAL®.

Tell your doctor if you become pregnant while you are taking OMEPRAL®.

Tell your doctor if your symptoms return.

Although OMEPRAL® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking OMEPRAL®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using OMEPRAL®.

Things you should not do

- Do not take OMEPRAL® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how OMEPRAL® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your OMEPRAL® in the blister pack until it is time to take them.
  If you take OMEPRAL® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking OMEPRAL® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with OMEPRAL® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, OMEPRAL® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking OMEPRAL®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking OMEPRAL®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What OMEPRAL® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

OMEPRAL® tablets do not contain gluten.

What OMEPRAL® looks like

OMEPRAL® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

OMEPRAL® 20 mg (blister pack) - AUST R 120594

Who distributes OMEPRAL®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany.

This leaflet was prepared in April 2023.

ACIMAX®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking ACIMAX®?

ACIMAX® contains the active ingredient omeprazole (as magnesium). ACIMAX® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using ACIMAX®? in the full CMI.

2. What should I know before I take ACIMAX®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use ACIMAX®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with ACIMAX® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take ACIMAX®?

- Take one ACIMAX® tablet each day, unless your doctor has told you otherwise.
- Swallow ACIMAX® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use ACIMAX®?

More instructions can be found in Section 4. How do I use ACIMAX®? in the full CMI.

5. What should I know while using ACIMAX®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using ACIMAX®. • Tell your doctor if you become pregnant while you are taking ACIMAX®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take ACIMAX® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how ACIMAX® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your ACIMAX® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using ACIMAX®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

ACIMAX®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using ACIMAX®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using ACIMAX®.**

Where to find information in this leaflet:

1. Why am I taking ACIMAX®?

ACIMAX® contains the active ingredient omeprazole (as magnesium). ACIMAX® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

ACIMAX® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

ACIMAX® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

ACIMAX® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

ACIMAX® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

ACIMAX® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When ACIMAX® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

ACIMAX® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

ACIMAX® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

ACIMAX® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that ACIMAX® is addictive.

2. What should I know before I take ACIMAX®?

Warnings

Do not take ACIMAX® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by ACIMAX®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to ACIMAX® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take ACIMAX® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take ACIMAX® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in ACIMAX® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take ACIMAX® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with ACIMAX® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by ACIMAX® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take ACIMAX®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect ACIMAX®.

4. How do I take ACIMAX®?

How much to take

- Take one ACIMAX® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of ACIMAX® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of ACIMAX® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use ACIMAX® until your doctor tells you to stop.

When to take ACIMAX®

- Take ACIMAX® at about the same time each day.
- Keeping a regular time for taking ACIMAX® will help to remind you to take it.
- ACIMAX® can be taken with food or on an empty stomach.

How to take ACIMAX®

- Swallow ACIMAX® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking ACIMAX® for as long as your doctor recommends.
  In most patients, ACIMAX® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking ACIMAX® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use ACIMAX®

ACIMAX® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much ACIMAX®

If you think that you have used too much ACIMAX®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using ACIMAX®?

Things you should do

Take ACIMAX® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking ACIMAX®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking ACIMAX®.

Tell your doctor if you become pregnant while you are taking ACIMAX®.

Tell your doctor if your symptoms return.

Although ACIMAX® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking ACIMAX®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using ACIMAX®.

Things you should not do

- Do not take ACIMAX® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how ACIMAX® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your ACIMAX® in the blister pack until it is time to take them.
  If you take ACIMAX® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking ACIMAX® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with ACIMAX® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, ACIMAX® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking ACIMAX®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking ACIMAX®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What ACIMAX® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

ACIMAX® tablets do not contain gluten.

What ACIMAX® looks like

ACIMAX® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

ACIMAX® 20 mg (blister pack) - AUST R 67306

Who distributes ACIMAX®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany.

This leaflet was prepared in April 2023~~November 2022~~.

LOSEC®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking LOSEC®?

LOSEC® contains the active ingredient omeprazole (as magnesium). LOSEC® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using LOSEC®? in the full CMI.

2. What should I know before I take LOSEC®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use LOSEC®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with LOSEC® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take LOSEC®?

- Take one LOSEC® tablet each day, unless your doctor has told you otherwise.
- Swallow LOSEC® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use LOSEC®?

More instructions can be found in Section 4. How do I use LOSEC®? in the full CMI.

5. What should I know while using LOSEC®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using LOSEC®. • Tell your doctor if you become pregnant while you are taking LOSEC®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take LOSEC® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how LOSEC® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your LOSEC® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using LOSEC®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

LOSEC®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using LOSEC®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using LOSEC®.**

Where to find information in this leaflet:

1. Why am I taking LOSEC®?

LOSEC® contains the active ingredient omeprazole (as magnesium). LOSEC® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

LOSEC® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

LOSEC® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

LOSEC® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

LOSEC® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

LOSEC® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When LOSEC® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

LOSEC® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

LOSEC® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

LOSEC® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that LOSEC® is addictive.

2. What should I know before I take LOSEC®?

Warnings

Do not take LOSEC® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by LOSEC®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to LOSEC® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take LOSEC® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take LOSEC® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in LOSEC® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take LOSEC® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with LOSEC® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by LOSEC® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take LOSEC®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect LOSEC®.

4. How do I take LOSEC®?

How much to take

- Take one LOSEC® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of LOSEC® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of LOSEC® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use LOSEC® until your doctor tells you to stop.

When to take LOSEC®

- Take LOSEC® at about the same time each day.
- Keeping a regular time for taking LOSEC® will help to remind you to take it.
- LOSEC® can be taken with food or on an empty stomach.

How to take LOSEC®

- Swallow LOSEC® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking LOSEC® for as long as your doctor recommends.
  In most patients, LOSEC® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking LOSEC® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use LOSEC®

LOSEC® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon

as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much LOSEC®

If you think that you have used too much LOSEC®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using LOSEC®?

Things you should do

Take LOSEC® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking LOSEC®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking LOSEC®.

Tell your doctor if you become pregnant while you are taking LOSEC®.

Tell your doctor if your symptoms return.

Although LOSEC® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking LOSEC®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using LOSEC®.

Things you should not do

- Do not take LOSEC® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how LOSEC® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your LOSEC® in the blister pack until it is time to take them.
  If you take LOSEC® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking LOSEC® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with LOSEC® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, LOSEC® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking LOSEC®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking LOSEC®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What LOSEC® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

LOSEC® tablets do not contain gluten.

What LOSEC® looks like

LOSEC® 10 mg tablets are light pink, oblong shaped, marked with 10 mg on one side and a logo on the other side.

LOSEC® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

LOSEC® 10 mg (blister pack) - AUST R 63414

LOSEC® 20 mg (blister pack) - AUST R 63416

Who distributes LOSEC®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

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This leaflet was prepared in April 2023~~November 2022~~.

OMEPRAL®

Consumer Medicine Information (CMI) summary

The full CMI on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I taking OMEPRAL®?

OMEPRAL® contains the active ingredient omeprazole (as magnesium). OMEPRAL® is used to treat: the symptoms of reflux oesophagitis or reflux disease; peptic ulcers; peptic ulcers associated with helicobacter pylori infection; peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs); and a rare condition called Zollinger-Ellison syndrome.

For more information, see Section 1. Why am I using OMEPRAL®? in the full CMI.

2. What should I know before I take OMEPRAL®?

Do not use if you have ever had an allergic reaction to omeprazole magnesium or any of the ingredients listed at the end of the CMI.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

For more information, see Section 2. What should I know before I use OMEPRAL®? in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with OMEPRAL® and affect how it works.

A list of these medicines is in Section 3. What if I am taking other medicines? in the full CMI.

4. How do I take OMEPRAL®?

- Take one OMEPRAL® tablet each day, unless your doctor has told you otherwise.
- Swallow OMEPRAL® whole with a glass of water. Do not crush or chew the tablets.
- If you have difficulty swallowing the tablets, follow the instructions in Section 4. How do I use OMEPRAL®?

More instructions can be found in Section 4. How do I use OMEPRAL®? in the full CMI.

5. What should I know while using OMEPRAL®?

Things you should do	• Remind any doctor, dentist or pharmacist you visit that you are using OMEPRAL®. • Tell your doctor if you become pregnant while you are taking OMEPRAL®. • Tell your doctor if your symptoms return.
Things you should not do	• Do not take OMEPRAL® to treat any other complaints unless your doctor tells you to. • Do not stop taking your medicine or change the dosage without checking with your doctor.
Driving or using machines	• Be careful before you drive or use any machines or tools until you know how OMEPRAL® affects you.
Drinking alcohol	• Tell your doctor if you drink alcohol.
Looking after your medicine	• Keep it in a cool, dry place where the temperature stays below 25°C. • Keep your OMEPRAL® in the blister pack until it is time to take them.

For more information, see Section 5. What should I know while using OMEPRAL®? in the full CMI.

6. Are there any side effects?

Mild side effects include: constipation, nausea or vomiting, diarrhoea, wind, stomach pain, headache, dizziness, skin rash, itchy skin, dry or sore mouth.
Serious side effects (Call your doctor straight away, or go straight to the Emergency Department) include: swelling of the face, lips, mouth, tongue or throat, shortness of breath or difficulty in breathing, skin reaction (which may include rash, itching, redness, blistering or peeling of the skin) especially in sun-exposed areas with joint pain, ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals, blood in the urine, swelling of hands, feet or ankles, yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

For more information, including what to do if you have any side effects, see Section 6. Are there any side effects? in the full CMI.

OMEPRAL®

Active ingredient(s): *omeprazole magnesium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using OMEPRAL®. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using OMEPRAL®.**

Where to find information in this leaflet:

1. Why am I taking OMEPRAL®?

OMEPRAL® contains the active ingredient omeprazole (as magnesium). OMEPRAL® is a type of medicine called a proton-pump inhibitor. It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place. This does not stop food being digested in the normal way.

Reflux Oesophagitis

OMEPRAL® is used to treat the symptoms of reflux oesophagitis or reflux disease.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

OMEPRAL® is also taken to help stop reflux oesophagitis coming back or relapsing.

Peptic Ulcers

OMEPRAL® is used to treat peptic ulcers.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

These ulcers can be caused by too much acid being made in the stomach.

OMEPRAL® is also used to help stop gastric or duodenal ulcers coming back.

Peptic Ulcers Associated with Helicobacter pylori Infection

OMEPRAL® is used to treat peptic ulcers associated with helicobacter pylori infection.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach.

When OMEPRAL® is taken with antibiotics, they work to kill the bacterium and let your ulcer heal. You may need further treatment with antibiotics.

Peptic Ulcers Associated with Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

OMEPRAL® is used to treat peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Some peptic ulcers are caused by taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs), a type of medicine used to treat pain or inflammation.

OMEPRAL® is also used to heal and prevent ulcers associated with NSAIDs.

Zollinger-Ellison Syndrome

OMEPRAL® is also used to treat a rare condition called Zollinger-Ellison syndrome.

This syndrome is -where the stomach produces large amounts of acid, much more than in ulcers or reflux disease.

There is no evidence that OMEPRAL® is addictive.

2. What should I know before I take OMEPRAL®?

Warnings

Do not take OMEPRAL® if:

- you are allergic to omeprazole, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicine containing a proton pump inhibitor.
- Always check the ingredients to make sure you can use this medicine.
  Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- you are also taking cilostazol.
  Please check with your doctor or pharmacist if you are taking cilostazol. This medicine will be affected by OMEPRAL®.
- the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.
  If it has expired or is damaged, return it to your pharmacist for disposal.

Check with your doctor if you have:

- allergies to any other medicines, foods, dyes or preservatives.
- take any medicines for any other condition.
- any problems with your liver.

- any other medical conditions.
- been diagnosed with osteoporosis.
- ever had a skin reaction after treatment with a medicine similar to OMEPRAL® that reduces stomach acid.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. Are there any side effects?

Pregnancy and breastfeeding

Do not take OMEPRAL® if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

Check with your doctor if you are pregnant or intend to become pregnant.

It is not known if it is safe for you to take OMEPRAL® while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

It is not known if your baby can take in OMEPRAL® from breast milk if you are breastfeeding.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Do not take OMEPRAL® if you are taking the following medicine:

- cilostazol - a medicine used to treat intermittent claudication.

Some medicines may interfere with OMEPRAL® and affect how it works.

- phenytoin - a medicine used to treat epilepsy or fits.
- warfarin and clopidogrel - medicines used to prevent blood clots.
- digoxin - a medicine used to treat heart conditions.
- diazepam - a medicine used to treat anxiety and some other conditions.
- St John's wort - a herbal remedy used to treat mood disorders.
- ketoconazole, itraconazole, voriconazole - medicines used to treat fungal infection.
- clarithromycin or rifampicin - medicines used to treat infections.
- atazanavir and nelfinavir - medicines used to treat viral infections such as HIV.
- tacrolimus and mycophenolate mofetil - medicines used to assist in organ transplants.
- methotrexate - a medicine used to treat arthritis and some types of cancer.
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by OMEPRAL® or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your doctor can tell you what to do if you are taking any other medicines.

If you have not told your doctor about any of these things, tell them before you take OMEPRAL®.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect OMEPRAL®.

4. How do I take OMEPRAL®?

How much to take

- Take one OMEPRAL® tablet each day, unless your doctor has told you otherwise.
- **Adults:** The dose of OMEPRAL® is usually 20 mg a day. The dose may vary from 10 mg to 40 mg a day depending on what condition you are being treated for and how severe it is.
- **Children (1 year or older):** The dose of OMEPRAL® is 10 mg a day for children 10 to 20 kg. This dose may be increased to 20 mg if required. For children more than 20 kg the dose is 20 mg a day. This dose may be increased to 40 mg if required.
- Follow the instructions provided and use OMEPRAL® until your doctor tells you to stop.

When to take OMEPRAL®

- Take OMEPRAL® at about the same time each day.
- Keeping a regular time for taking OMEPRAL® will help to remind you to take it.
- OMEPRAL® can be taken with food or on an empty stomach.

How to take OMEPRAL®

- Swallow OMEPRAL® whole with a glass of water. Do not crush or chew the tablets.
- If the tablets are chewed or crushed, they will not work properly.
- Keep taking OMEPRAL® for as long as your doctor recommends.
  In most patients, OMEPRAL® relieves symptoms rapidly and healing is usually complete within 4 weeks. Continue taking OMEPRAL® for as long as your doctor tells you to.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water or fruit juice. Mineral water, carbonated fruit juices, or other liquids are not suitable.
2. Gently mix the tablet and liquid by stirring, taking care not to crush the tablet.
3. Stir until the tablet disperses into little pellets.
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets.
5. Rinse the glass with half a glass of water and drink.

If you forget to use OMEPRAL®

OMEPRAL® should be used regularly at the same time each day. If you miss your dose at the usual time, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed.

If you use too much OMEPRAL®

If you think that you have used too much OMEPRAL®, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using OMEPRAL®?

Things you should do

Take OMEPRAL® exactly as your doctor has prescribed.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking OMEPRAL®.

Tell all doctors, dentists and pharmacists who are treating you that you are taking OMEPRAL®.

Tell your doctor if you become pregnant while you are taking OMEPRAL®.

Tell your doctor if your symptoms return.

Although OMEPRAL® can heal ulcers successfully, it may not prevent them recurring at a later date.

If you need to have any medical tests while you are taking OMEPRAL®, tell your doctor.

It may affect the results of some tests.

Remind any doctor, dentist or pharmacist [you visit that you are using OMEPRAL®.

Things you should not do

- Do not take OMEPRAL® to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if they have the same condition as you.
- Do not stop taking your medicine or change the dosage without checking with your doctor.
  If you stop taking it suddenly or change the dose, your condition may worsen or you may have unwanted side effects.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how OMEPRAL® affects you.

Drinking alcohol

Tell your doctor if you drink alcohol.

Looking after your medicine

- Keep your OMEPRAL® in the blister pack until it is time to take them.
  If you take OMEPRAL® out of the blister pack they will not keep well.
- Keep it in a cool, dry place where the temperature stays below 25°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:

- in the bathroom or near a sink, or
- in the car or on windowsills.

Keep it where young children cannot reach it.

When to discard your medicine

If your doctor tells you to stop taking OMEPRAL® or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Getting rid of any unwanted medicine

If you no longer need to use this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
These side effects are usually mild. • constipation • nausea or vomiting • diarrhoea • wind • stomach pain • headache • dizziness • skin rash, itchy skin • dry or sore mouth	**Speak to your doctor if you have any of these less serious side effects and they worry you.**

Serious side effects

Serious side effects	What to do
These are serious side effects that may require medical attention. Serious side effects are rare. • muscle pain or weakness, joint pain • "pins and needles" • changes in sleep patterns • mood changes, confusion or depression • blurred vision • increase in breast size (males) • fever • increased bruising • increased sweating • hair loss • tremor • pain or indigestion that occurs during treatment with OMEPRAL® • you begin to vomit blood or food • you pass black (blood-stained) motions • treatment > 3 month possibly decrease magnesium blood levels resulting in fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate • low magnesium blood levels may cause decrease of potassium or calcium levels in blood	**Tell your doctor immediately if you notice any of these serious side effects.**
These are very serious side effects. You may need urgent medical attention or hospitalisation. These side effects are rare. • swelling of the face, lips, mouth, tongue or throat which may cause difficulty in breathing • shortness of breath or difficulty in breathing • skin reaction which may include rash, itching, redness, blistering or peeling of the skin • ulcers, blisters or bleeding of the lips, eyes, mouth, nose and genitals • blood in the urine • swelling of hands, feet or ankles • signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite • skin reaction, especially in sun-exposed areas, with joint pain	**Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Occasionally, OMEPRAL® may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

When taking OMEPRAL®, inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

Tell your doctor if your reflux symptoms return after you stop taking OMEPRAL®.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What OMEPRAL® contains

Active ingredient (main ingredient)	Omeprazole magnesium
Other ingredients (inactive ingredients)	Glyceryl monostearate Hyprolose Hypromellose Magnesium stearate Methacrylic acid copolymer Microcrystalline cellulose Synthetic paraffin Macrogol 6000 Polysorbate 80 Crospovidone Sodium stearylfumarate Purified talc Titanium dioxide Triethyl citrate Sodium hydroxide Sugar spheres (maize starch and sucrose) Iron oxide red (CI77491)

	Iron oxide yellow (CI77492)

Do not take this medicine if you are allergic to any of these ingredients.

OMEPRAL® tablets do not contain gluten.

What OMEPRAL® looks like

OMEPRAL® 20 mg tablets are pink, oblong shaped, marked with 20 mg on one side and a logo on the other side.

Australian Registration Numbers:

OMEPRAL® 20 mg (blister pack) - AUST R 120594

Who distributes OMEPRAL®

Pharmaco (Australia) Ltd

Level 13, 465 Victoria Avenue

Chatswood NSW 2067

Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany.

This leaflet was prepared in April 2023~~November 2022~~.

From: s22
To: s22 s47G
Subject: 9D(2) SRR without data + 9D(3) MEC approval letter with attachments - PM-2023-01952-1-1 omeprazole magnesium (ACIMAX/LOSEC/OMEPRAL) - Pharmaco Australia Ltd - 22 June 2023 [SEC=OFFICIAL]
Date: Thursday, 22 June 2023 6:54:51 PM
Attachments: [D23-5494672] 9D(2) SRR without data + 9D(3) MEC approval letter with attachments - PM-2023-01952-1-1 omeprazole magnesium (ACIMAX LOSEC OMEPRAL) - Pharmaco Australia Ltd - 22 June 2023.PDF

Dear s22

Please find attached the approval letter for the above submission.

Could you please reply to this email to confirm receipt of the attached letter.

Kind regards,

s22
s22
Pharmacist Evaluation Section
Prescription Medicines Authorisation Branch
Email: s22 @health.gov.au

Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

The Managing Director
Pharmaco Australia Ltd
Locked Bag 1009
GORDON NSW 2072

Clinical File: 2011/008817
PI File: 2010/018780
Submission No.: PM-2023-01952-1-1
Data: e006250 - (0017)

Attention: s22
s47G

Dear Sir/Madam,

REQUEST UNDER s. 9D(2) FOR SAFETY-RELATED VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

REQUEST UNDER s. 9D(3) FOR VARIATION TO THE ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

I refer to your request under subsections 9D(2) and 9D(3) of the *Therapeutic Goods Act 1989* (the Act) dated 26 April 2023 to vary the entry of:

- AUST R 120594 - OMEPRAL omeprazole (as magnesium) 20mg tablet blister pack
- AUST R 63414 - LOSEC omeprazole 10mg (as magnesium) tablet blister pack
- AUST R 63416 - LOSEC omeprazole 20mg (as magnesium) tablet blister pack
- AUST R 67306 - ACIMAX omeprazole (as magnesium) 20mg tablet blister pack

(referred to hereinafter as the product(s)) in the Australian Register of Therapeutic Goods (the ARTG) as described in **Attachment 2a**.

Approval of such a request would result in a decision by the Secretary under subsection 25AA(4) to reflect any variation made under subsection 9D(2) and 9D(3).

Subsections 9D(2), 9D(3), 25AA(4) of the Act can be found online at the following link: **https://www.legislation.gov.au/Series/C2004A03952**

Decision

As delegate of the Secretary of the Department of Health and Aged Care, I am:

- under subsection 9D(2) and 9D(3) of the Act, varying the information in the entry of the product(s) in the ARTG as requested
- under subsection 25AA(4) of the Act, approving the text of the approved Product Information (PI) for the product(s) to reflect this as set out in the version at **Attachment 2a and 2b** on the basis that the only changes made to the most recently approved PI were those set out in your request. This approval is based on the evaluation of the information provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Date of effect

The date of effect of the variation is the date of this approval letter. The "Date of revision" included in the PI is to be the date of this letter.

Action required of you

The approved PI at **Attachment 2b** must be lodged with the TGA **within 2 weeks** of the date of approval of the variation. If the related Consumer Medicine Information (CMI) document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI.

The documents must be lodged in the TGA eBusiness Services system. Information on how to lodge these documents is available at www.ebs.tga.gov.au. The documents must be in text PDF format – scanned PDF documents will **not** be accepted by the system.

Review rights

Details of review rights for the decision under subsection 9D(2), 9D(3) and 25AA(4) are provided at **Attachment 1**.

Your obligations in relation to Product Information etc.

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the Consumer Medicine Information must comply with the requirements set out in the Therapeutic Goods Regulations 1990, which includes the obligation to ensure the CMI that must be supplied with the medicine is 'consistent with' the approved PI.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully,

Electronically signed and authorised by
s22 [redacted]
s22 [redacted]

Pharmacist Evaluation Section
Prescription Medicines Authorisation Branch
Email: s22 [redacted]@health.gov.au

22 June 2023

Attachments:

1. Review rights
2. Approved product information for:
   a. ACIMAX/LOSEC/OMEPRAL omeprazole (as magnesium) tablet (changes highlighted)
   b. ACIMAX/LOSEC/OMEPRAL omeprazole (as magnesium) tablet (clean)

Attachment 1

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**decision.review@health.gov.au**'

Subject: "**<insert name of person/company making request>** - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "… - Email 1 of 3", "… - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

AUSTRALIAN PRODUCT INFORMATION
ACIMAX® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ACIMAX Tablets is omeprazole magnesium, a substituted benzimidazole. ACIMAX is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ACIMAX Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the ACIMAX logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACIMAX Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACIMAX Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: ACIMAX Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with ACIMAX Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, ACIMAX Tablets 10 mg once daily. If needed, this dose should be increased to ACIMAX Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is ACIMAX Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is ACIMAX Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: ACIMAX Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	ACIMAX Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	ACIMAX Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of ACIMAX Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ACIMAX. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when ACIMAX Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ACIMAX Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ACIMAX is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs

within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of ACIMAX Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was~~ere~~ markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ACIMAX tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ACIMAX is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

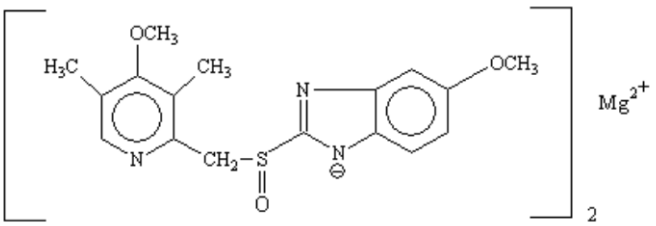
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

18 August 1999

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
LOSEC® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg and 20 mg tablets containing omeprazole magnesium 10.3 mg and 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs

within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was~~ere~~ markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

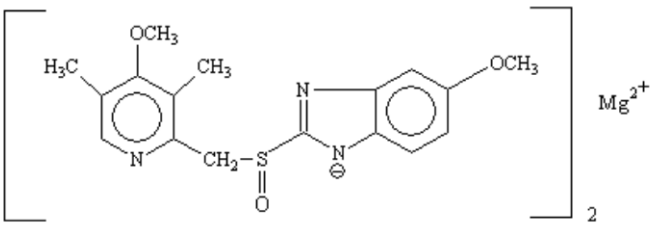
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
OMEPRAL® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in OMEPRAL Tablets is omeprazole magnesium, a substituted benzimidazole. OMEPRAL is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

OMEPRAL Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the OMEPRAL logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OMEPRAL Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

OMEPRAL Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: OMEPRAL Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with OMEPRAL Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, OMEPRAL Tablets 10 mg once daily. If needed, this dose should be increased to OMEPRAL Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is OMEPRAL Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is OMEPRAL Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: OMEPRAL Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	OMEPRAL Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	OMEPRAL Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of OMEPRAL Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse ~~a~~effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping OMEPRAL. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g.

diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when OMEPRAL Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant

treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OMEPRAL Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)~~Interstitial nephritis~~
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OMEPRAL is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is

dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of OMEPRAL Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests

were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two--year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects wasere markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical reSection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124--week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OMEPRAL tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate,

sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

OMEPRAL is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

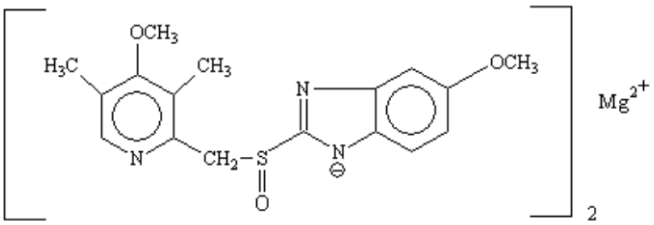
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue
Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

1 November 2005

10. DATE OF REVISION

~~21 November 2022~~

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
ACIMAX® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ACIMAX Tablets is omeprazole magnesium, a substituted benzimidazole. ACIMAX is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ACIMAX Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the ACIMAX logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACIMAX Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

ACIMAX Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: ACIMAX Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with ACIMAX Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, ACIMAX Tablets 10 mg once daily. If needed, this dose should be increased to ACIMAX Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: ACIMAX Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, ACIMAX Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is ACIMAX Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is ACIMAX Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is ACIMAX Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: ACIMAX Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	ACIMAX Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	ACIMAX Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of ACIMAX Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ACIMAX. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when ACIMAX Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ACIMAX Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ACIMAX is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of ACIMAX Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ACIMAX tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ACIMAX is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

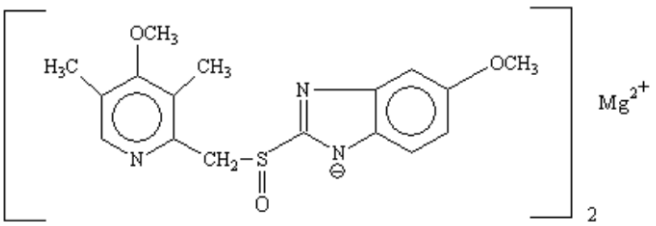
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

18 August 1999

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
LOSEC® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg and 20 mg tablets containing omeprazole magnesium 10.3 mg and 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via

CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in

transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate

embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

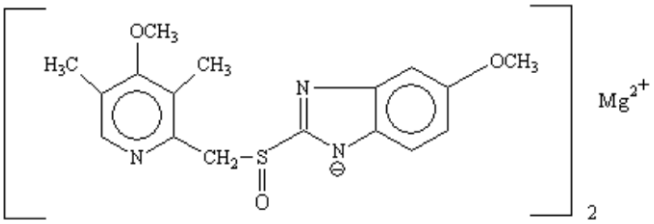
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue

Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

AUSTRALIAN PRODUCT INFORMATION
OMEPRAL® TABLETS
omeprazole magnesium
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in OMEPRAL Tablets is omeprazole magnesium, a substituted benzimidazole. OMEPRAL is available in 20 mg tablets containing omeprazole magnesium 20.6 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

OMEPRAL Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the OMEPRAL logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OMEPRAL Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

   The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

   The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

OMEPRAL Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: OMEPRAL Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with OMEPRAL Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, OMEPRAL Tablets 10 mg once daily. If needed, this dose should be increased to OMEPRAL Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: OMEPRAL Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, OMEPRAL Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is OMEPRAL Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is OMEPRAL Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is OMEPRAL Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: OMEPRAL Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

Weight	*Dose*
10-20 kg	OMEPRAL Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	OMEPRAL Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of OMEPRAL Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping OMEPRAL. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g.

diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when OMEPRAL Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant

treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m^2 basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OMEPRAL Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia
Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children). Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders

Uncommon: Insomnia
Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm
Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)
Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia
Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise
Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

OMEPRAL is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is

dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with Helicobacter pylori

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4

SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of OMEPRAL Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests

were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

b) H_2-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

c) Surgical reSection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124-week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OMEPRAL tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, titanium dioxide, triethyl citrate,

sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

OMEPRAL is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

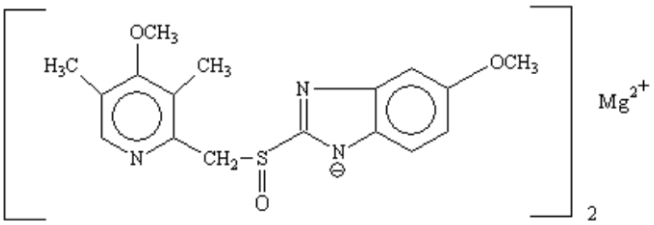
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue
Chatswood NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

1 November 2005

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Inclusion of Renal Impairment
4.8	Update of rare side effect concerning renal and urinary disorders

From: s22
To: s22
Cc: s22
Subject: RE: 9D(2) SRR without data + 9D(3) MEC approval letter with attachments - PM-2023-01952-1-1 omeprazole magnesium (ACIMAX/LOSEC/OMEPRAL) - Pharmaco Australia Ltd - 22 June 2023 [SEC=OFFICIAL]
Date: Friday, 23 June 2023 12:18:02 PM

Dear s22

Thank you for your email, confirming receipt of the approval letter.

Kind regards,
s22

s22
s47G

From: s22 <s22 @health.gov.au>
Sent: Thursday, June 22, 2023 4:55 PM
To: s22 s47G
Subject: 9D(2) SRR without data + 9D(3) MEC approval letter with attachments - PM-2023-01952-1-1 omeprazole magnesium (ACIMAX/LOSEC/OMEPRAL) - Pharmaco Australia Ltd - 22 June 2023 [SEC=OFFICIAL]

Dear s22

Please find attached the approval letter for the above submission.

Could you please reply to this email to confirm receipt of the attached letter.

Kind regards,

s22
s22
s22
Pharmacist Evaluation Section
Prescription Medicines Authorisation Branch
Email: s22 @health.gov.au

Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
PO Box 100

Woden ACT 2606
www.tga.gov.au

This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all of the legislative requirements are met.

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