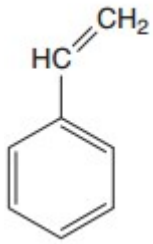
s22 [redacted]

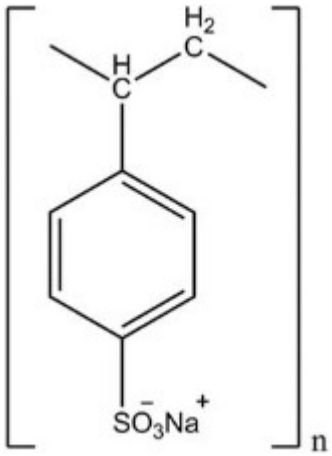
From: s22 [redacted] on behalf of Toxicology
Sent: Friday, 8 June 2018 12:57 PM
To: s22 [redacted]
Subject: RE: Re: Safety concern re Duromine interaction with PPI's and carcinogenicity CRM:0036627 [DLM=For-Official-Use-Only]

The sender refers to a positive carcinogenicity findings for styrene in mice.
Animal and human carcinogenicity data for this compound have been reviewed by the World Health Organization's International Agency for Research on Cancer, and **styrene is classified by the IARC as "probably carcinogenic to humans" (Group 2A).**

This is the chemical structure of styrene:



Amberlite IRP69 is derived from styrene, but is not styrene. **Styrene is not used as an excipient in DUROMINE.**
The resin used in DUROMINE is sodium polystyrene sulfonate (a sulfonated copolymer of styrene and divinylbenzene). That is, many units of this structure joined together (*i.e.*, polymerised) in a chain:



While carcinogenicity studies have not been performed with sodium polystyrene sulfonate, the chemical and toxicological properties of this molecule are massively different from styrene. When polymerised, there is no metabolism and no absorption and the molecule is pharmacologically inert (apart from exchange of sodium for other cations). The long history of apparent safe clinical use with regard to tumourigenicity supports there being no cause for concern for carcinogenicity for this compound.

s22 [redacted]
Principal Toxicologist
Scientific Evaluation Branch

Phone: s22 [redacted]

Email: s22 @tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: s22
Sent: Friday, 8 June 2018 11:00 AM
To: s22
Subject: FW: Re: Safety concern re Duromine interaction with PPI's and carcinogenicity CRM:0036627 [DLM=For-Official-Use-Only]

Hi s22,
As discussed on the phone earlier this week, would you mind having a look to see if you hold any information about the carcinogenicity of Amberlite IRP69 (referred to in the attached email). Do you think there is a basis for the health practitioners concerns regarding cancer risk (see attached emails)
We discussed this issue at the SIU team meeting yesterday.

Kind regards
s22

s22
Senior Pharmacist
Signal Investigation Unit
Pharmacovigilance and Special Access Branch

Phone: s22
Email: s22 @health.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

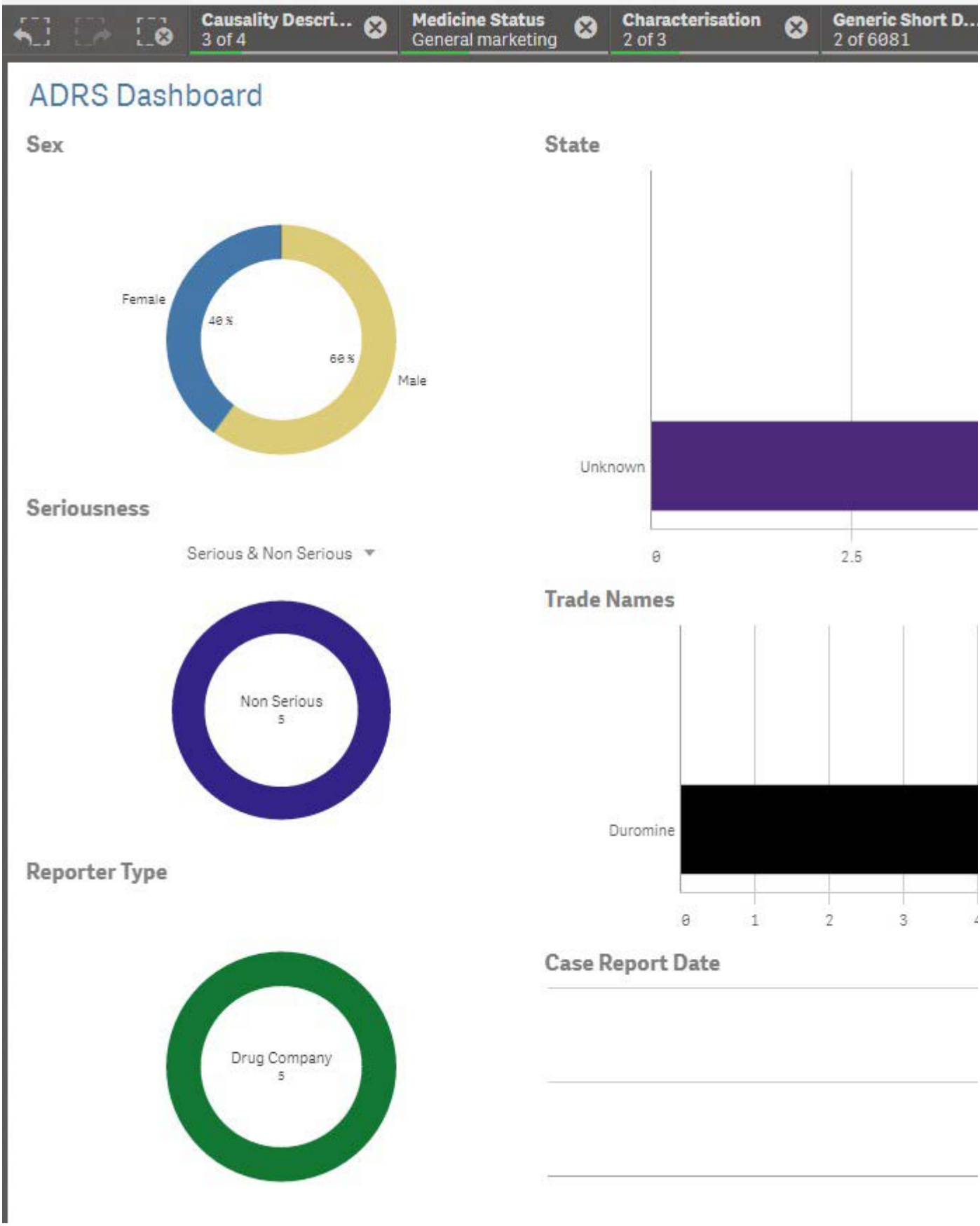
I acknowledge the traditional custodians of the lands and waters where we live and work, and pay my respects to elders past, present and future.

From: s22 **On Behalf Of** ADR Reports
Sent: Monday, 4 June 2018 3:00 PM
To: s22
Subject: FW: Re: Safety concern re Duromine interaction with PPI's CRM:0036627 [SEC=UNCLASSIFIED]

Hi s22

I have just attached the 1st two emails the concerned GP sent through.

Looking at Qlik we have 5 cases of drug ineffective dating back 1999 and 2000.



https://www.fishersci.com/shop/msdsproxy?productName=AC301311000&productDescription=AMBERLITE+IRP69+ION+EXCH+100G&catNo=AC301311000&vendorId=VN00032119&storeId=10652

Thanks, do you want some help into looking at some stuff?

s2
s22

Medical Officer
Adverse Event and Medicine Defect Section
Pharmacovigilance and Special Access Branch
Email: s22 @tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

From: TGA Info
Sent: Friday, 1 June 2018 3:36 PM
To: ADR Reports
Subject: FW: Re: Safety concern re Duromine interaction with PPI's [SEC=No Protective Marking] [SEC=UNCLASSIFIED] CRM:0036627

Good afternoon

Please find attached an email from s22 - email: s22 @outlook.com - for your follow up and response. If your area is not the appropriate area to respond to this email please let us know.

If you are responding directly to an external enquiry, you are responsible for ensuring that the TGA customer service standards are met.

Please ensure that any internal correspondence is deleted prior to sending the response.

If your area does not have access to a generic email address, the RAS can send approved responses on your behalf from info@tga.gov.au, provided there is sufficient time for the service standards to be met.

Kind regards

Regulatory Assistance Section
Regulatory Services and Improvement Branch

Phone: 1800 020 653 Fax: 02 6203 1605
Email: info@tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

---------- Original Message ----------
From: s22 @outlook.com;

Received: 29/05/2018 1:55 PM
To: TGA Info (null);
Subject: Re: Safety concern re Duromine interaction with PPI's [SEC=No Protective Marking]

Please replace my earlier email with the corrected copy appended below. I have deleted information which may not be correct (based on a misreading of a search result, copied below).

Corrected copy:

From: s22 [redacted]
Sent: Tuesday, 29 May 2018 10:14 AM
To: info@tga.gov.au
Subject: Safety concern re Duromine interaction with PPI's

Dear Sir,

Duromine capsules (including Metermine) contain beads bound to phentermine base. The rate of drug elution from the beads depends on the concentration of ions in the gut. PPI's such as omeprazole and esomeprazole can cause achlorhydria with less ions in the stomach which could reduce phentermine release from the beads. This has never been studied but seems possible.

It is noted that the relevant patient population (obese people) are likely to suffer from reflux hence are likely to be taking a PPI.

This could become a serious issue if a generic of Duromine is ever approved which is not similarly affected by PPI's, since the products won't be bioequivalent and blood levels could fluctuate significantly if a patient taking a PPI switches from one phentermine product to another.

It is noted that Duromine has never been formally evaluated by the TGA since it was launched about 60 years ago. Perhaps it's time for this old drug to be evaluated.

I believe iNova should be asked to comment on the bioavailability and safety of Duromine when taken with a PPI and the PI should be updated to publicise the interaction if confirmed.

Regards,
s22 [redacted]

Australian Government
Department of Health
Therapeutic Goods Administration

The Managing Director
AstraZeneca Pty Ltd
Alma Road
North Ryde NSW 2113
Australia

TRIM ref: R15/162033

Attention: Regulator Affairs Manager (LOSEC/Omeprazole magnesium)

Dear Sir/Madam

RE: LOSEC (Omeprazole sodium ARTG 63414, 63416, 63418) – request to update the Australian Product Information (PI) following a (FDA) drug safety update

The Signal Investigation (Medicines) Unit (SIU) of the Therapeutic Goods Administration (TGA) Post-market Surveillance Branch (PMSB) has received notification from the US Food and Drug Administration (FDA) of an update to the Product Label for Omeprazole sodium.

The changes to the Product Label are summarised below.

Warnings and precautions

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 an idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

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

Interactions with other medicines

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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.

Following an evaluation of the US Product Label update by the TGA, an update to the Australian PI is requested. It is requested that you update the Precautions and Drug Interactions section of the Losec® PI in line with the changes to the US Product Label.

The requested changes may be made as a safety-related request (SRR) under the provisions of Section 9D(2) of the Therapeutic Goods Act 1989. This should be done as soon as possible and no later than one month from the date of this letter. To facilitate processing, please include a copy of this letter with the notification.

Please advise me by email, with a copy to the Signal Investigation Coordinator at si.coordinator@tga.gov.au, when you have submitted your SRR and include a copy of the proposed PI.

Thank you for your attention to this matter.

Yours sincerely,

s22

Departmental Officer
Signal Investigation (Medicines) Unit
Post-market Surveillance Branch
Therapeutic Goods Administration (TGA) Australia

Friday 27th February 2015

Australian Government
Department of Health
Therapeutic Goods Administration

The Managing Director
AstraZeneca Pty Ltd
5 Alma Road
North Ryde NSW
Australia

TRIM ref: R15/290511

Attention: Regulator Affairs Manager (LOSEC/Omeprazole)

Dear Sir/Madam

RE: LOSEC (Omeprazole sodium ARTG 63414, 63416, 63418) – follow up for request to update the Australian Product Information (PI)

The Signal Investigation (Medicines) Unit (SIU) of the Therapeutic Goods Administration (TGA) Post-market Surveillance Branch (PMSB) wrote to you on 27th February 2015, alerting you of updates to the US Food and Drug Administration (FDA) Product Label for omeprazole.

Please provide a written (email preferred) response to this letter, indicating whether the safety related request (SRR) has been submitted to the TGA as requested, with a proposed PI and a submission number. If this has not yet been completed, please submit an SRR under the provisions of Section 9D(2) of the Therapeutic Goods Act 1989 within 2 weeks of the date of this letter.

If you have any questions regarding this request, please contact me on (02) s22 or s22 @tga.gov.au

I have attached a copy of the original letter for your reference

Yours sincerely,

s22
Pharmacist
Signal Investigation (Medicines) Unit
Post-market Surveillance Branch
Therapeutic Goods Administration (TGA) Australia

Monday 20th April 2015

From: s22
To: Regulatory Outcomes Stream
Cc: s22
Subject: FW: TRIM: RE: SAP Proton Pump Inhibitors and Tubulointerstitial Nephritis and Renal Failure [SEC=OFFICIAL]
Date: Thursday, 8 August 2024 12:26:00 PM
Attachments: image002.png
image003.png

Dear RORMS

An assessment of the safety issue "PPIs and Tubulointerstitial Nephritis and Renal Failure" (2015/008656) has been completed and a PI update for rabeprazole is recommended. Please see below for more details, and let me know if any further information is required.

Many thanks,
s22

From: s22 @health.gov.au>
Sent: Wednesday, August 7, 2024 7:14 AM
To: s22 @Health.gov.au>
Subject: TRIM: RE: SAP Proton Pump Inhibitors and Tubulointerstitial Nephritis and Renal Failure [SEC=OFFICIAL]

s22, Thank you for this SAP. I agree with your recommendation.

Kind Regards

s22
Medical Officer- Medicines Surveillance and Signal Investigation Section

Medicines Regulation Division | Therapeutic Goods Administration
Pharmacovigilance Branch
Australian Government Department of Health and Aged Care
E: s22 @health.gov.au
Location: Level 11, 11 Waymouth Street
MDP:117, GPO Box 9848, Adelaide SA 5001, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @Health.gov.au>
Sent: Tuesday, August 6, 2024 11:51 AM
To: s22 @health.gov.au>
Subject: SAP Proton Pump Inhibitors and Tubulointerstitial Nephritis and Renal Failure [SEC=OFFICIAL]

Hi s22,

Here is another SAP I would appreciate your input on, thank you!

Safety Issue	Omeprazole and rabeprazole, tubulointerstitial nephritis and renal failure
Signal Source	On 12 May 2024, Medis Pharma notified TGA of PRAC PSUR Assessment reports published by EMA • in December 2022, regarding **omeprazole** and renal impairment (D24-1872627), • in August 2022 for **rabeprazole** and renal impairment (D24-1835020). CMDh endorsed amendments to the EMA SmPC sections 4.4 and 4.8 (see below for more details) for both of these products.
Current Information	
• **Aus PI**	**Omeprazole** (last revised 13 November 2023, D24-3303807): Section 4.4 Special Warnings and Precautions for Use • 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. Section 4.8 Adverse Effects-->Renal and urinary disorders • Rare: tubulointerstitial nephritis (with possible progression to renal failure) **Rabeprazole** (last revised 5 May 2023, D24-3303860) • Section 4.4 wording similar to that for omeprazole • Section 4.8 Post-Marketing Experience: interstitial nephritis listed • Note there is no warning on progression to renal failure *While pantoprazole and lansoprazole were not included in these notifications, review of the PIs showed that tubulointerstitial nephritis and risk of renal failure are listed.
• **Relevant COR documents**	**Health Canada Health Product InfoWatch May 2024** (D24-3180301) • 'Warnings and Precautions,' 'Adverse Reactions (Post-Market)' and 'Patient Information' sections of Product Monograph for **omeprazole** updated with risk of acute tubulointerstitial nephritis, noting that it may occur at any point during therapy, can progress to renal failure, and should be discontinued if TIN suspected. **CMDh recommendations for EMA SmPC Omeprazole and Rabeprazole** (attachments in notifications) Section 4.4 • "Acute tubulointerstitial nephritis (TIN) has been observed in patients taking [name of PPI] and may occur at any point during…therapy." • "[TIN] can progress to renal failure." • "[Name of PPI] should be discontinued in case of suspected TIN". Section 4.8 • Specify tubulointerstitial nephritis and possible progression to renal failure Rabeprazole SmPC (available via Ireland's Health Products Regulatory Authority, last revised December 2022, D24-3304195) lists risk of acute tubulointerstitial nephritis with possible progression to renal failure, frequency rare.
• **AEMS**	**Case reports** Search of AEMS under default bookmark, generic name 'rabeprazole sodium' and reaction term 'tubulointerstitial nephritis' yielded 35 reports. • 'Renal failure' was also coded for 5 of these cases (Case IDs 272625, 214371, 236376, 236389 and 272625), although concomitant medications were taken in these cases. • 2 reports (Case IDs 192348, 209412) included 'renal failure' as past medical history. Addition of reaction term 'renal failure' yielded 9 more cases (where tubulointerstitial nephritis was NOT co-reported) **DPAR** • Renal failure PRR 14.0 • Tubulointerstitial nephritis PRR 53.2
• **Vigilyze**	Search under global view, active ingredient 'rabeprazole' and PTs 'renal failure,' 'tubulointerstitial nephritis' • 3971 cases total • Tubulointerstitial nephritis: 1153 cases, IC025 6.7 • Renal failure: 3084 cases, IC025 5.6
Recommendation	REFERRAL TO REGULATORY OUTCOMES AND RISK MANAGEMENT SECTION (RORMS) is recommended at this time, to update the rabeprazole PI in alignment with that of other proton pump inhibitors, listing risk of tubulointerstitial nephritis and risk of progression to renal failure. • There are cases of rabeprazole associated with tubulointerstitial nephritis and renal failure in Australia, and disproportionality flags for both PTs on AEMS and Vigilyze. • Including warning on progression to renal failure in rabeprazole PI characterises the potential severity of TIN.

Warm regards,
s22

s22
Medical Officer – Medicines Surveillance and Signal Investigation Section
Pharmacovigilance Branch

Medicines Regulation Division | Therapeutic Goods Administration
Australian Government Department of Health and Aged Care
Ph: s22
E: s22 @health.gov.au
s22

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22
To: Signal Investigation Coordinator
Cc: s22 ; 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' s22 @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
66 Talavera Road, Macquarie Park, NSW 2113, Australia
T: s22 F: s22 M: s22
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 (s47G(1)(a)), with s47G(1)(a) . On 23 February 2023, AstraZeneca sent the reviewed joint DHCPL for NEXIUM/AXIAGO to s47G(1)(a) for SAHPRA's submission. The joint DHCPL was submitted by s47G(1)(a) 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: s22 @astrazeneca.com; s22 @astrazeneca.com; s22 @astrazeneca.com; s22 @astrazeneca.com s22 @astrazeneca.com; s22 @astrazeneca.com
Cc: s22 ; Regulatory Outcomes Stream
Subject: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]
Date: Friday, 27 September 2024 9:28:19 AM
Attachments: image001.png
image002.png
image004.png

Dear s22 and s22

This correspondence notifies you of the TGA's conclusion to include the risk of tubulointerstitial nephritis (TIN) with possible progression to renal failure in the Product Information (PI) for esomeprazole. The TGA expects AstraZeneca to update the Australian Product Information (PI) and Consumer Medicines Information (CMI) to include this new safety information for the following products:

ARTG No	Products
74133	NEXIUM esomeprazole 20mg (as magnesium trihydrate) tablet blister pack
74134	NEXIUM esomeprazole 40mg (as magnesium trihydrate) tablet blister pack
96678	NEXIUM IV esomeprazole 40mg (as sodium) powder for injection vial
135726	NEXIUM esomeprazole 10 mg (as magnesium trihydrate) enteric coated granules for oral suspension sachet
281690	NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack
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) 40 mg tablet blister pack
202464	REFEXXIN esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
349670	ESOPREZE esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack
349671	ESOPREZE esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack

The TGA's conclusion to update the Australian PI is based on the following evidence:

Evidence	Summary
TGA Adverse Events Management System (AEMS)	• A search of the AEMS database on 26 September 2024 using search terms 'esomeprazole', 'esomeprazole magnesium trihydrate' and PT 'tubulointerstitial nephritis' found 47 local cases. PT renal failure was co-reported in 3 cases and PT acute kidney injury was co-reported in 7 cases. The presence of Australian cases indicates there is a local signal for esomeprazole and TIN with possible progression to renal failure.
WHO adverse events database (Vigilyze)	• A positive IC_{025} value of 6.1 for 'esomeprazole' and PT 'tubulointerstitial nephritis' was obtained from Vigilyze on 26 September 2024. Of the 3738 cases reported, 3684 were reported as serious including 511 cases with a fatal outcome, 60 cases of a positive dechallenge, 1 case of a positive rechallenge and 192 cases where esomeprazole was the sole suspected drug. Notably, PT renal failure was co-reported in 1557 cases (41.7% of total cases) and PT acute kidney injury was co-reported in 2980 cases (79.7% of total cases).
Overseas product information and/or regulatory action	• The EU SmPC for esomeprazole includes *interstitial nephritis; in some patients, renal failure has been reported concomitantly* in Section 4.8. The Australian population is not dissimilar to that of Europe and inclusion of this risk in the Australian PI will align with this international labelling.
Additional information	• The Australian PI for other proton pump inhibitors (PPIs), including LOSEC (omeprazole), SOMAC (pantoprazole) and ZOTON (lansoprazole), already contain the risk of tubulointerstitial nephritis with possible progression to renal failure in Section 4.8. The Australian PI for LOSEC (omeprazole) also includes this risk in Section 4.4. The additional warning of possible progression to renal failure appropriately characterises the potential severity of TIN to healthcare professionals and ensures consistency across Australian PIs for PPIs. • A literature search using PubMed on 23 September 2024 retrieved 6 articles in support of this signal.[1,2,3,4,5,6] Articles highlighted the importance of timely diagnosis and prompt withdrawal of the offending agent to prevent potentially life-threatening renal failure.

Required action:
Identified safety issues require prompt risk mitigation to ensure ongoing public safety. I therefore request that you submit a Safety-Related Request (SRR) application to the Prescription Medicines Authorisation Branch (PMAB) under the provisions of section 9D(2) of the *Therapeutic Goods Act 1989* to effect the necessary changes outlined below, **no later than 25 October 2024.** (Wording to be added is blue and underlined.)

FOR NEXIUM and NEXIUM IV

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Acute tubulointerstitial nephritis
Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue esomeprazole if acute tubulointerstitial nephritis develops.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

Clinical trials and post-marketing data

…

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

FOR NEXIUM Hp7

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.

-

-

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

…

Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience

…

System Organ Class	Frequency	Event
…		-
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)

When you are completing the online variations e-form for a SRR application through the TBS portal, please include the following text in the comment section ***"This SRR application is at the request of the Pharmacovigilance Branch."*** Please also include this text in the cover letter of your dossier.

All sponsors of esomeprazole products are expected to update the PI and CMI documents on this issue, irrespective of marketing status. This requirement to keep product information documents up to date with safety information, irrespective of marketing status, is outlined on the TGA website under 'Pharmacovigilance obligations of medicine sponsors' (https://www.tga.gov.au/pharmacovigilance-obligations-medicine-sponsors).

Sponsors can download the Public Case Detail (PCD) and Case Line Listing (CLL) reports relevant to this medicine and adverse event from the Adverse Event Management System (AEMS) portal. Further information on how to access and use the AEMS portal can be found on the TGA website in the AEMS guidance for sponsors: AEMS guidance for sponsors | Therapeutic Goods Administration (TGA).

Please do not hesitate to contact me via email s22 @health.gov.au should you require further information. Please submit all written correspondence to me by email.

Thank you for your attention to this matter.

Kind regards

s22

References

[1]Sanchez-Alamo B, Cases-Corona C, Fernandez-Juarez G. Facing the Challenge of Drug-Induced Acute Interstitial Nephritis. Nephron. 2023;147(2):78-90. doi:10.1159/000525561

[2]Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26(4):545-553. doi:10.1111/j.1365-2036.2007.03407.x

[3]Weir MR. Proton Pump Inhibitors and Kidney Disease: Fact or Fiction?. Am J Nephrol. 2024;55(4):499-508. doi:10.1159/000538755

[4]Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton). 2006;11(5):381-385. doi:10.1111/j.1440-1797.2006.00651.x

[5]Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. Clin Gastroenterol Hepatol. 2006;4(5):597-604. doi:10.1016/j.cgh.2005.11.004

[6]Härmark L, van der Wiel HE, de Groot MC, van Grootheest AC. Proton pump inhibitor-induced acute interstitial nephritis. Br J Clin Pharmacol. 2007;64(6):819-823. doi:10.1111/j.1365-2125.2007.02927.x

s22
Pharmacist
Regulatory Outcomes and Risk Management Section (RORMS)
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 12, 130 George St, Parramatta NSW 2150
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22
To: s22 s22 s22 ; s22 s22
Cc: s22 ; Regulatory Outcomes s22
Subject: RE: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]
Date: Wednesday, 23 October 2024 2:02:28 PM
Attachments: image001.png
image002.png
image004.png
safety-query-response-tga-nexium.pdf

Dear s22

Hope you are well.

Please find attached document AstraZeneca's response to TGA request on Nexium and TIN.
Please do not hesitate to contact me for any questions.

Kind regards,

s22
Regulatory Affairs Associate

AstraZeneca
66 Talavera Road, Macquarie Park, NSW 2113, Australia
T: s22
s22 @astrazeneca.com

From: s22 @astrazeneca.com>
Sent: Friday, September 27, 2024 10:16 AM
To: s22 @Health.gov.au>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 s22 @astrazeneca.com>; s22 @astrazeneca.com>
Cc: s22 @Health.gov.au>; Regulatory Outcomes Stream s22 @Health.gov.au>; s22 @astrazeneca.com>; s22 @astrazeneca.com>
Subject: RE: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]

Hello s22

Thank you very much for your correspondence regards Nexium and TIN.
AstraZeneca will provide you with a response by the requested due date.

With best wishes

s22

s22
Patient Safety Manager

AstraZeneca Australia and New Zealand, Patient Safety
66 Talavera Road, Macquarie Park, 2113
T: s22 M: s22 s22 @astrazeneca.com | https://contactazmedical.astrazeneca.com

---

From s @Health.gov.au>
Sent: Friday, September 27, 2024 9:28 AM
To: s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 s22 @astrazeneca.com>; s22 @astrazeneca.com>
Cc: s22 @Health.gov.au>; Regulatory Outcomes Stream s22 @Health.gov.au>
Subject: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]

Dear s22 and s22

This correspondence notifies you of the TGA's conclusion to include the risk of tubulointerstitial nephritis (TIN) with possible progression to renal failure in the Product Information (PI) for esomeprazole. The TGA expects AstraZeneca to update the Australian Product Information (PI) and Consumer Medicines Information (CMI) to include this new safety information for the following products:

ARTG No	Products
74133	NEXIUM esomeprazole 20mg (as magnesium trihydrate) tablet blister pack
74134	NEXIUM esomeprazole 40mg (as magnesium trihydrate) tablet blister pack
96678	NEXIUM IV esomeprazole 40mg (as sodium) powder for injection vial
135726	NEXIUM esomeprazole 10 mg (as magnesium trihydrate) enteric coated granules for oral suspension sachet
281690	NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack
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) 40 mg tablet blister pack
202464	REFEXXIN esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
349670	ESOPREZE esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack
349671	ESOPREZE esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack

The TGA's conclusion to update the Australian PI is based on the following evidence:

Evidence	Summary
TGA Adverse Events Management System (AEMS)	• A search of the AEMS database on 26 September 2024 using search terms 'esomeprazole', 'esomeprazole magnesium trihydrate' and PT 'tubulointerstitial nephritis' found 47 local cases. PT renal failure was co-reported in 3 cases and PT acute kidney injury was co-reported in 7 cases. The presence of Australian cases indicates there is a local signal for esomeprazole and TIN with possible progression to renal failure.
WHO adverse events database (Vigilyze)	• A positive IC_{025} value of 6.1 for 'esomeprazole' and PT 'tubulointerstitial nephritis' was obtained from Vigilyze on 26 September 2024. Of the 3738 cases reported, 3684 were reported as serious including 511 cases with a fatal outcome, 60 cases of a positive dechallenge, 1 case of a positive rechallenge and 192 cases where esomeprazole was the sole suspected drug. Notably, PT renal failure was co-reported in 1557 cases (41.7% of total cases) and PT acute kidney injury was co-reported in 2980 cases (79.7% of total cases).
Overseas product information and/or regulatory action	• The EU SmPC for esomeprazole includes *interstitial nephritis; in some patients, renal failure has been reported concomitantly* in Section 4.8. The Australian population is not dissimilar to that of Europe and inclusion of this risk in the Australian PI will align with this international labelling.
Additional information	• The Australian PI for other proton pump inhibitors (PPIs), including LOSEC (omeprazole), SOMAC (pantoprazole) and ZOTON (lansoprazole), already contain the risk of tubulointerstitial nephritis with possible progression to renal failure in Section 4.8. The Australian PI for LOSEC (omeprazole) also includes this risk in Section 4.4. The additional warning of possible progression to renal failure appropriately characterises the potential severity of TIN to healthcare professionals and ensures consistency across Australian PIs for PPIs. • A literature search using PubMed on 23 September 2024 retrieved 6 articles in support of this signal.[1,2,3,4,5,6] Articles highlighted the importance of timely diagnosis and prompt withdrawal of the offending agent to prevent potentially life-threatening renal failure.

Required action:

Identified safety issues require prompt risk mitigation to ensure ongoing public safety. I therefore request that you submit a Safety-Related Request (SRR) application to the Prescription Medicines Authorisation Branch (PMAB) under the provisions of section 9D(2) of the *Therapeutic Goods Act 1989* to effect the necessary changes outlined below, **no later than 25 October 2024.** (Wording to be added is blue and underlined.)

FOR NEXIUM and NEXIUM IV

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

Clinical trials and post-marketing data

…

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

FOR NEXIUM Hp7

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.

-

-

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

…

Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience

…

System Organ Class	Frequency	Event
…		-
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)

When you are completing the online variations e-form for a SRR application through the TBS portal, please include the following text in the comment section ***"This SRR application is at the request of the Pharmacovigilance Branch."*** Please also include this text in the cover letter of your dossier.

All sponsors of esomeprazole products are expected to update the PI and CMI documents on this issue, irrespective of marketing status. This requirement to keep product information documents up to date with safety information, irrespective of marketing status, is outlined on the TGA website under 'Pharmacovigilance obligations of medicine sponsors' (https://www.tga.gov.au/pharmacovigilance-obligations-medicine-sponsors).

Sponsors can download the Public Case Detail (PCD) and Case Line Listing (CLL) reports relevant to this medicine and adverse event from the Adverse Event Management System (AEMS) portal. Further information on how to access and use the AEMS portal can be found on the TGA website in the AEMS guidance for sponsors: AEMS guidance for sponsors | Therapeutic Goods Administration (TGA).

Please do not hesitate to contact me via email s22 @health.gov.au should you require further information. Please submit all written correspondence to me by email.

Thank you for your attention to this matter.

Kind regards
s22

References

[1]Sanchez-Alamo B, Cases-Corona C, Fernandez-Juarez G. Facing the Challenge of Drug-Induced Acute Interstitial Nephritis. Nephron. 2023;147(2):78-90. doi:10.1159/000525561

[2]Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26(4):545-553. doi:10.1111/j.1365-2036.2007.03407.x

[3]Weir MR. Proton Pump Inhibitors and Kidney Disease: Fact or Fiction?. Am J Nephrol. 2024;55(4):499-508. doi:10.1159/000538755

[4]Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton). 2006;11(5):381-385. doi:10.1111/j.1440-1797.2006.00651.x

[5]Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. Clin Gastroenterol Hepatol. 2006;4(5):597-604. doi:10.1016/j.cgh.2005.11.004

[6]Härmark L, van der Wiel HE, de Groot MC, van Grootheest AC. Proton pump inhibitor-induced acute interstitial nephritis. Br J Clin Pharmacol. 2007;64(6):819-823. doi:10.1111/j.1365-2125.2007.02927.x

s22
Pharmacist
Regulatory Outcomes and Risk Management Section (RORMS)
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T s22 | E: s22 @health.gov.au
Location: Level 12, 130 George St, Parramatta NSW 2150
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

Response Document

NEXIUM (esomeprazole)

Date: 21 October 2024

NEXIUM/ESOPREZE/AXAGON/REFEXXIN (Esomeprazole)

AstraZeneca's Response to Therapeutic Goods Administration's (TGA) Safety related request to update the Product Information (PI) for NEXIUM (Oral and IV formulation) to include the risk of tubulointerstitial nephritis (TIN) with possible progression to renal failure

TABLE OF CONTENTS

1 INTRODUCTION

On 27 September 2024, AstraZeneca received a Safety-Related Request from the Therapeutic Goods Administration's (TGA) under the provisions of Section 9D(2) of the Therapeutic Goods Act 1989 to update the risk of tubulointerstitial nephritis (TIN) with possible progression to renal failure in Section 4.4 (Special Warnings and Precautions for use) and Section 4.8 (Adverse Effects [Undesirable Effects]) of the Nexium Product Information (PI) and Consumer Medicines Information (CMI) for both oral and intravenous (IV) formulation.

The purpose of this document is to provide a response to the TGA safety related request.

2 TGA SAFETY RELATED REQUEST AND ASTRAZENECA'S RESPONSES

2.1 TGA request to update section 4.4 and 4.8 for NEXIUM and NEXIUM IV and oral PI

Wordings to be added are blue and underlined.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Acute tubulointerstitial nephritis
Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue esomeprazole if acute tubulointerstitial nephritis develops.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):
Clinical trials and post-marketing data

Renal and urinary disorders
Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

AstraZeneca response: AstraZeneca acknowledges the TGA's query and respectfully disagrees with the recommendation to reword warning on interstitial nephritis in Section 4.4 and inclusion of the proposed text "(*with possible progression to renal failure)"* in Section 4.8 of the Australian PI and CMI. Interstitial nephritis is a well-recognized adverse drug reaction (ADR) of proton pump inhibitors (PPIs) including NEXIUM. It is AstraZeneca's view that the clinical course and manifestations of interstitial nephritis as well as potential occurrence of acute renal failure as a result of interstitial nephritis is well known to prescribers.

Moreover, AstraZeneca is of the opinion that the renal safety profile of NEXIUM has not changed in any meaningful way over recent years (in particular, since AstraZeneca's comprehensive review of the topic in 2020) and the previous understanding of this ADR

remains the same. Additionally, AstraZeneca is routinely monitoring this topic as per internal process and based on the review of the cases from AstraZeneca's global safety database and literature till 10 September 2024, no new significant information has been identified on progression of Interstitial nephritis to renal failure.

Additionally, AstraZeneca is of the opinion that the change in term to 'acute tubulointerstitial nephritis' will not change the current understanding of the pathophysiology of acute interstitial nephritis by prescribing physicians. Hence, AstraZeneca suggests retaining the term acute interstitial nephritis in Section 4.4 and Section 4.8 of the Australian PI.

AstraZeneca comment on the articles referred to by TGA is provided below:

The literature references shared by TGA included four case series (Geevasinga et al 2006, Härmark et al 2007, Simpson et al 2006, Sierra et al 2007) of acute tubulointerstitial nephritis (ATIN) due to PPI therapy. These publications from 2006-2007 had been previously reviewed by AstraZeneca and taken into consideration in our safety position on this condition. Sanchez-Alamo et al 2023 is a review article focussing on drug-induced ATIN, but not specific to PPIs. The authors reviewed a number of studies that suggest that PPIs may be associated with an increased risk of chronic kidney disease (CKD). However, they point out that these studies have major limitations such as modest associations and considerable potential for residual confounders. As with other types of acute kidney injury, drug-induced ATIN, especially when diagnosis is delayed or missed, can result in incomplete renal recovery and permanent kidney damage. This has been highlighted in various ATIN case series published around 15 to 20 years ago and there is no new relevant information presented here. Weir et al 2024 is a review article looking at the evidence linking ATIN and CKD. Many of the studies reviewed in this paper had substantial statistical and epidemiologic weaknesses, e.g. not adjusting for baseline kidney function, concomitant medication use, or medical comorbidities as well as likely residual confounding. The author concludes that there is insufficient evidence to link PPI exposure with the development or progression of CKD.

Based on these publications, it is AstraZeneca's opinion that there is no new relevant information or change in the current safety profile of this drug class.

Therefore, it is AstraZeneca's opinion that the ADR of interstitial nephritis in Section 4.8 adequately informs prescribers of the current clinical knowledge on the topic, and that further label changes are not warranted (i.e. to Sections 4.4 and Section 4.8 of the Australian PI and CMI).

2.2 TGA request to update section 4.4 and 4.8 for NEXIUM Hp7

Wordings to be added are blue and underlined.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience

System Organ Class	Frequency	Event
…		
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)

AstraZeneca's Response: Please refer to our response above (Section 2.1). Since NEXIUM Hp7 is a secondary brand of NEXIUM (Primary brand), label updates will be followed as per primary brand.

3 REFERENCES

Geevasinga et al 2006
Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton Pump Inhibitors and Acute Interstitial Nephritis. CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2006;4:597–604.

Simpson et al 2006
Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton). 2006;11(5):381-85.

Härmark et al 2007
Härmark L, van der Wiel HE, de Groot MC, van Grootheest AC. Proton pump inhibitor-induced acute interstitial nephritis. Br J Clin Pharmacol. 2007 Dec;64(6):819-23.

Sierra et al 2007
Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26(4):545-53.

Sanchez-Alamo et al 2023
Sanchez-Alamo B, Cases-Corona C, Fernandez-Juarez G. Facing the Challenge of Drug-Induced Acute Interstitial Nephritis. Nephron. 2023;147(2):78-90.

Weir et al 2024
Weir MR. Proton Pump Inhibitors and Kidney Disease: Fact or Fiction?. Am J Nephrol. 2024;55(4):499-508.

From: s22
To: s22
Cc: s22 ; Regulatory Outcomes Stream; s22 ; s22 ; s22 ; s22 s22 s22
Subject: RE: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]
Date: Tuesday, 29 October 2024 11:26:37 AM
Attachments: image001.png
image002.png
image004.png

Dear s2

Thank you for your response regarding safety-related changes to the Product Information (PI) for NEXIUM, NEXIUM IV and NEXIUM Hp7 relating to tubulointerstitial nephritis (with possible progression to renal failure). We appreciate your considered response to the TGA request.

We are undertaking a class update to ensure consistency across the Australian PIs of all proton pump inhibitors. The inclusion of tubulointerstitial nephritis (with possible progression to renal failure) will increase awareness of medical practitioners, assisting with timely diagnosis and management of this severe and potentially life-threatening outcome. We consider that a listed warning in the PI will provide a clear warning to health professionals rather than an implied understanding of the adverse effect.

Based on its inclusion in the PI of a comparable overseas regulator, the reasons set out in our email of 27 September 2024 and those outlined above, we reiterate the TGA's initial request to update Sections 4.4 and 4.8 of the PI for the products.

Required PI changes:
After consideration of the further evidence provided by AstraZeneca, the TGA respectfully declines AstraZeneca's request to keep the NEXIUM, NEXIUM IV and NEXIUM Hp7 PIs unchanged. Therefore, we request AstraZeneca to submit a Safety-Related Request (SRR) application to the Prescription Medicines Authorisation Branch (PMAB) under the provisions of section 9D(2) of the Therapeutic Goods Act 1989 to effect the necessary changes outlined below, **no later than 12 November 2024.**

FOR NEXIUM and NEXIUM IV

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Acute tubulointerstitial nephritis
Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue esomeprazole if acute tubulointerstitial nephritis develops.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):
Clinical trials and post-marketing data
…
Renal and urinary disorders
Very rare: tubulointerstitial nephritis (with possible progression to renal failure)
-

FOR NEXIUM Hp7

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Acute tubulointerstitial nephritis
Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.
-
-
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):
…
Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience
…

System Organ Class	Frequency	Event
…		-
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)

When you are completing the online variations e-form for a SRR application through the TBS portal, please include the following text in the comment section ***"This SRR application is at the request of the Pharmacovigilance Branch."*** Please also include this text in the cover letter of your dossier.

Kind regards
s22

s22
Pharmacist
Regulatory Outcomes and Risk Management Section (RORMS)
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 12, 130 George St, Parramatta NSW 2150
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @astrazeneca.com>
Sent: Wednesday, 23 October 2024 2:02 PM
To: s22 @astrazeneca.com>; s22 @Health.gov.au>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>
Cc: s22 @Health.gov.au>; Regulatory Outcomes Stream s22 @Health.gov.au>; s22 @astrazeneca.com>
Subject: RE: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear s22

Hope you are well.

Please find attached document AstraZeneca's response to TGA request on Nexium and TIN.
Please do not hesitate to contact me for any questions.

Kind regards,

s22
Regulatory Affairs Associate

AstraZeneca
66 Talavera Road, Macquarie Park, NSW 2113, Australia
T: s22
s22 @astrazeneca.com

Please consider the environment before printing this e-mail

From: s22 @astrazeneca.com>
Sent: Friday, September 27, 2024 10:16 AM
To: s22 @Health.gov.au>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 <s22 @astrazeneca.com>; s22 @astrazeneca.com>
Cc: s22 @Health.gov.au>; Regulatory Outcomes Stream s22 @Health.gov.au>; s22 s22 @astrazeneca.com>; s22 @astrazeneca.com>
Subject: RE: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]

Hello s22

Thank you very much for your correspondence regards Nexium and TIN.
AstraZeneca will provide you with a response by the requested due date.

With best wishes

s22

s22

Patient Safety Manager

AstraZeneca Australia and New Zealand, Patient Safety
66 Talavera Road, Macquarie Park, 2113
T: s22 M: +s22 @astrazeneca.com | https://contactazmedical.astrazeneca.com

From: s22 @Health.gov.au>
Sent: Friday, September 27, 2024 9:28 AM
To: s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>; s22 @astrazeneca.com>
Cc: s22 @Health.gov.au>; Regulatory Outcomes Stream s22 @Health.gov.au>
Subject: Product Information Update Notification: esomeprazole and tubulointerstitial nephritis (with possible progression to renal failure) [SEC=OFFICIAL]

Dear s22 and s22

This correspondence notifies you of the TGA's conclusion to include the risk of tubulointerstitial nephritis (TIN) with possible progression to renal failure in the Product Information (PI) for esomeprazole. The TGA expects AstraZeneca to update the Australian Product Information (PI) and Consumer Medicines Information (CMI) to include this new safety information for the following products:

ARTG No	Products
74133	NEXIUM esomeprazole 20mg (as magnesium trihydrate) tablet blister pack
74134	NEXIUM esomeprazole 40mg (as magnesium trihydrate) tablet blister pack
96678	NEXIUM IV esomeprazole 40mg (as sodium) powder for injection vial
135726	NEXIUM esomeprazole 10 mg (as magnesium trihydrate) enteric coated granules for oral suspension sachet
281690	NEXIUM Hp7 esomeprazole tablet, amoxicillin capsule, clarithromycin tablet composite pack
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) 40 mg tablet blister pack
202464	REFEXXIN esomeprazole (as magnesium trihydrate) 20 mg tablet blister pack
349670	ESOPREZE esomeprazole 20 mg (as magnesium trihydrate) tablet blister pack
349671	ESOPREZE esomeprazole 40 mg (as magnesium trihydrate) tablet blister pack

The TGA's conclusion to update the Australian PI is based on the following evidence:

Evidence	Summary
TGA Adverse Events Management System (AEMS)	• A search of the AEMS database on 26 September 2024 using search terms 'esomeprazole', 'esomeprazole magnesium trihydrate' and PT 'tubulointerstitial nephritis' found 47 local cases. PT renal failure was co-reported in 3 cases and PT acute kidney injury was co-reported in 7 cases. The presence of Australian cases indicates there is a local signal for esomeprazole and TIN with possible progression to renal failure.
WHO adverse events database (Vigilyze)	• A positive IC_{025} value of 6.1 for 'esomeprazole' and PT 'tubulointerstitial nephritis' was obtained from Vigilyze on 26 September 2024. Of the 3738 cases reported, 3684 were reported as serious including 511 cases with a fatal outcome, 60 cases of a positive dechallenge, 1 case of a positive rechallenge and 192 cases where esomeprazole was the sole suspected drug. Notably, PT renal failure was co-reported in 1557 cases (41.7% of total cases) and PT acute kidney injury was co-reported in 2980 cases (79.7% of total cases).
Overseas product information and/or regulatory action	• The EU SmPC for esomeprazole includes *interstitial nephritis; in some patients, renal failure has been reported concomitantly* in Section 4.8. The Australian population is not dissimilar to that of Europe and inclusion of this risk in the Australian PI will align with this international labelling.
Additional information	• The Australian PI for other proton pump inhibitors (PPIs), including LOSEC (omeprazole), SOMAC (pantoprazole) and ZOTON (lansoprazole), already contain the risk of tubulointerstitial nephritis with possible progression to renal failure in Section 4.8. The Australian PI for LOSEC (omeprazole) also includes this risk in Section 4.4. The additional warning of possible progression to renal failure appropriately characterises the potential severity of TIN to healthcare professionals and ensures consistency across Australian PIs for PPIs. • A literature search using PubMed on 23 September 2024 retrieved 6 articles in support of this signal.[1,2,3,4,5,6] Articles highlighted the importance of timely diagnosis and prompt withdrawal of the offending agent to prevent potentially life-threatening renal failure.

Required action:
Identified safety issues require prompt risk mitigation to ensure ongoing public safety. I therefore request that you submit a Safety-Related Request (SRR) application to the Prescription Medicines Authorisation Branch (PMAB) under the provisions of section 9D(2) of the *Therapeutic Goods Act 1989* to effect the necessary changes outlined below, **no later than 25 October 2024.** (Wording to be added is blue and underlined.)

FOR NEXIUM and NEXIUM IV

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

Clinical trials and post-marketing data

…

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

FOR NEXIUM Hp7

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.

-

-

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS):

…

Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience

…

System Organ Class	Frequency	Event
…		-
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)

When you are completing the online variations e-form for a SRR application through the TBS portal, please include the following text in the comment section ***"This SRR application is at the request of the Pharmacovigilance Branch."*** Please also include this text in the cover letter of your dossier.

All sponsors of esomeprazole products are expected to update the PI and CMI documents on this issue, irrespective of marketing status. This requirement to keep product information documents up to date with safety information, irrespective of marketing status, is outlined on the TGA website under 'Pharmacovigilance obligations of medicine sponsors' (https://www.tga.gov.au/pharmacovigilance-obligations-medicine-sponsors).

Sponsors can download the Public Case Detail (PCD) and Case Line Listing (CLL) reports relevant to this medicine and adverse event from the Adverse Event Management System (AEMS) portal. Further information on how to access and use the AEMS portal can be found on the TGA website in the AEMS guidance for sponsors: AEMS guidance for sponsors | Therapeutic Goods Administration (TGA).

Please do not hesitate to contact me via email s22 @health.gov.au should you require further information. Please submit all written correspondence to me by email.

Thank you for your attention to this matter.

Kind regards

s22

References

[1]Sanchez-Alamo B, Cases-Corona C, Fernandez-Juarez G. Facing the Challenge of Drug-Induced Acute Interstitial Nephritis. Nephron. 2023;147(2):78-90. doi:10.1159/000525561

[2]Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26(4):545-553. doi:10.1111/j.1365-2036.2007.03407.x

[3]Weir MR. Proton Pump Inhibitors and Kidney Disease: Fact or Fiction?. Am J Nephrol. 2024;55(4):499-508. doi:10.1159/000538755

[4]Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton). 2006;11(5):381-385. doi:10.1111/j.1440-1797.2006.00651.x

[5]Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. Clin Gastroenterol Hepatol. 2006;4(5):597-604. doi:10.1016/j.cgh.2005.11.004

[6]Härmark L, van der Wiel HE, de Groot MC, van Grootheest AC. Proton pump inhibitor-induced acute interstitial nephritis. Br J Clin Pharmacol. 2007;64(6):819-823. doi:10.1111/j.1365-2125.2007.02927.x

s22

Pharmacist
Regulatory Outcomes and Risk Management Section (RORMS)
Pharmacovigilance Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 12, 130 George St, Parramatta NSW 2150
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

AU-TGA-0000322592

Case details:

Original received date: 3/07/2013

Creation date: 3/07/2013

Date sent to WHO: 12/08/2013

Involves an unapproved product?: No

Unapproved product access:

Modified on: 23/06/2018

Decision Reason: Causality possible

Serious ICSR: No

Sender details:

Janssen Cilag

1-5 Khartoum Road

Macquarie Park NSW 2113

Sender type: Pharmaceutical Company

Sender's ICSR indentifier: s22 ANZ0354441

Patient details:

Patient initials: s22 ANZ0354441

Sex: Female

Weight:

Age: 92 (Year)

Date of birth:

State:

Ethnicity:

Reporter details:

,

Phone:

Case narrative:

s22 [redacted]

Reactions:

Preferred term	Onset date	End date	Outcome
Blood creatinine increased			Recovering/resolving
Chronic kidney disease			Recovering/resolving

Drug information:

Product name	Role characterisation	Action taken
TN006266 Pariet - Pariet	Suspect	Unknown

Active Ingredient/s

Rabeprazole sodium ( )

Dosage/s

Dose	Interval	Dose form	Route of admin	Start date	End date	Batch
Dose Unspecified			Oral			

Additional information

TN004812 Pariet GN002640 Rabeprazole Sodium

Product name	Role characterisation	Action taken
TN000857 Astrix 100 - Astrix 100	Concomitant	Unknown

Active Ingredient/s

Aspirin ( )

Dosage/s

Dose	Interval	Dose form	Route of admin	Start date	End date	Batch

Additional information

TN000524 Astrix 100 GN000241 Aspirin

Product name	Role characterisation	Action taken
TN002068 Citracal - Citracal	Concomitant	Unknown

Active Ingredient/s

Calcium citrate ( )

Dosage/s

Dose	Interval	Dose form	Route of admin	Start date	End date	Batch

Additional information

TN0850 Citracal GN004346 Calcium Citrate

Product name	Role characterisation	Action taken
TN003395 Fosamax - Fosamax	Concomitant	Unknown

Active Ingredient/s

alendronate sodium ( )

Dosage/s

Dose	Interval	Dose form	Route of admin	Start date	End date	Batch

Additional information

TN002550 Fosamax GN000074 Alendronate Sodium

Product name	Role characterisation	Action taken
TN005464 Noten - Noten	Concomitant	Unknown

Active Ingredient/s

Atenolol ( )

Dosage/s

Dose	Interval	Dose form	Route of admin	Start date	End date	Batch

Additional information

TN004490 Noten GN000246 Atenolol

Tests and procedures:

CIOMS FORM

Document 14

SUSPECT ADVERSE REACTION REPORT

Mfr. Control No. :AU-Eisai Inc-E3810- Cont...

I.REACTION INFORMATION

1.PATIENT INITIALS	1a.COUNTRY	2.DATE OF BIRTH DA	2.DATE OF BIRTH MO	2.DATE OF BIRTH YR	2a. AGE YRS	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
s22	AUSTRALIA				92	F			2013

7.+13. DESCRIBE REACTION(S) (include relevant test/lab data)

CHRONIC KIDNEY DISEASE (Chronic kidney disease (10064848), Renal failure chronic (10038444)) [v.16.0]
Protocol relatedness:
As per reporter:
As per company:

CREATININE INCREASE (Serum creatinine increased (10040233), Blood creatinine increased (10005483)) [v.16.0]
Protocol relatedness:
As per reporter:
As per company:

A spontaneous report was received from a health professional, concerning a 92 year-old female patient who experienced chronic kidney disease and serum Cr results increased while receiving rabeprazole for an unknown indication.

Cont...

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ RESULTS IN PERSISTENT OR SIGNIFICANT DISABILITY/ INCAPACITY
- ☐ CONGENITAL ANOMALY
- ☒ OTHER MEDICALLY IMPORTANT CONDITION

II.SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) Subject Unblinded :

PARIET (RABEPRAZOLE)(RABEPRAZOLE)

20.DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION: Oral

21.DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

17. INDICATIONS FOR USE

18. THERAPY DATES(From/To): /05/2009 - //2013

19. THERAPY DURATION: 4 Years

III.CONCOMITANT DRUGS AND HISTORY

22.CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

CITRACAL(CALCIUM CITRATE)	Unknown
ASTRIX(ACETYLSALICYLIC ACID)	Unknown
FOSAMAX(ALENDRONATE SODIUM)	Unknown
NOTEN(ATENOLOL)	Unknown

Cont...

23. OTHER RELEVANT HISTORY

No Risk Factor Available
NONE REPORTED

IV. MANUFACTURER

24a. NAME AND ADDRESS OF MANUFACTURER

Eisai Europe Ltd
Pharmacovigilance
European Knowledge Centre, Mosquito Way
Hatfield, Hertforshire UNITED KINGDOM

24b. MFR. CONTROL NO.: AU-Eisai Inc-E3810- Cont...

24c. DATE RECEIVED BY MANUFACTURER: 21/06/2013

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ☐ AUTHORITY
☒ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT: 02/07/2013

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOW UP ☐ FINAL

Initial Reporter:

AUSTRALIA

Cont... = Continuation attached sheet(s)

Document 14

Continuation Sheet for CIOMS report **Mfr. Control No. :AU-Eisai Inc-E3810- Cont...**

Describe Reaction(s)(Include relevant test/lab data) (Cont...)

s22 [redacted]

Suspect Drugs (Cont...)

Product-Reaction level

Seq.No. : 1
Drug : PARIET (RABEPRAZOLE)(RABEPRAZOLE)

Causality

1) CREATININE INCREASE (Serum creatinine increased (10040233), Blood creatinine increased (10005483)) [v.16.0]
Action(s) taken with drug : Drug discontinued
Causality as per reporter (Drug/Vaccine) : Not provided
Causality as per Mfr.(Drug/Vaccine) : Not assessable

Concomitant drugs (Cont...)

Seq.No. : 5
Drug : PARACETAMOL(PARACETAMOL)

24b. MFR. CONTROL NO.

AU-Eisai Inc-E3810-06499-SPO-AU

Company Remarks (Cont...)

s22 [redacted]

Additional information (continuation)

Lab Result :

Test name	Test date	Test result	Normal value	Classification
10040230	/ /2013	138		
	/ /2013	129		
	/ /2013	162		
	/ /2013	102		