Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for budesonide

Proprietary Product Name: Cortiment

Sponsor: Ferring Pharmaceuticals Pty Ltd

January 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee for Prescription Medicines
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AUC	Area under the plasma concentration time curve
AUC_{ss}	Area under the plasma concentration time curve steady state
AUC_{∞}	Area under the plasma concentration time curve from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration time curve from time 0 to t
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 to 24 h
CAI	Clinical Activity Index
CI	confidence interval
C_{max}	maximum concentration
CRP	C-reactive protein
CV	coefficient of variation
CYP3A	The 3A subfamily of cytochrome P450
ESR	erythrocyte sedimentation rate
EU	European Union
GCP	Good clinical practice
HPA axis	Hypothalamus pituitary adrenal axis
IBD	Inflammatory bowel disease
IBD QoL	Inflammatory Bowel Disease-Quality of Life
ITT	intent to treat
mane	in the morning
MRHD	maximum recommended highest dose
MMX	Multi-Matrix

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PP	per protocol
PSAB	Pharmacovigilance and Special Access Branch
PSUR	periodic safety update report
SAE	Serious adverse event
SBA	Summary Basis for Approval (FDA)
SD	Standard deviation
TEAEs	Treatment-emergent adverse events
TDS	three times daily
t½	Half life
T_{max}	time after administration of a drug when the maximum plasma concentration is reached
UC	Ulcerative colitis
UCDAI	Ulcerative Colitis Disease Activity Index
UK	United Kingdom
USAN	United States Adopted Name

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new dosage form and new indication)
Decision:	Approved
Date of decision:	27 August 2015
Date on ARTG	31 August 2015
Active ingredient:	Budesonide
Product name:	Cortiment
Sponsor's name and address:	Ferring Pharmaceuticals Pty Ltd Suite 2, Level 1, Building 1, 20 Bridge Street Pymble NSW 2073
Dose form:	Prolonged release tablet
Strength:	9 mg
Container:	Blister pack
Pack sizes:	10, 20, 30, 50, 60 and 80 modified release tablets
Approved therapeutic use:	*Cortiment prolonged-release tablets are indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient or not tolerated.*
Route of administration:	Oral
Dosage:	The recommended daily dose for induction of remission is one 9 mg tablet in the morning for up to 8 weeks.
ARTG number:	225849

Product background

This AusPAR describes the application by Ferring Pharmaceuticals (the sponsor) to register Cortiment for the following indication:

> *Cortiment prolonged-release tablets are indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC).*

Budesonide is a synthetic glucocorticoid with comparable anti-inflammatory effects to the conventional glucocorticoids. The majority of currently registered budesonide products are formulated as locally acting inhalation products (for treatment of asthma) and nasal spray products (for treatment of hay fever). Orally administered budesonide is rapidly and

almost completely absorbed, but systemic exposure to the drug, and its systemic effects are limited due to rapid and extensive clearance from the blood stream by pre-systemic metabolism. This occurs mainly by first pass hepatic metabolism, but also by metabolism within the gastrointestinal tract (GIT) wall; the extent of systemic absorption is only about 10 to 15 %. For this reason, budesonide is usually formulated into products intended to take advantage if its effects as a topical anti-inflammatory, which in the case of Cortiment is on the tissue lining of the lower GIT.

There are currently three budesonide products listed on the Australian Register of Therapeutic Goods (ARTG) (for topical) use in inflammatory bowel disease (IBD): Entocort 3 mg controlled ileal release capsules and Budenofalk 3 mg enteric capsules which are both for oral use in Crohn's disease as well as Budenofalk 2 mg foam enema, approved for rectal use in Ulcerative colitis (UC).

Crohn's disease can affect any part of the GIT, but most commonly the ileum and the adjoining ascending colon. Therefore the Entocort and Budenofalk oral capsules, are designed to delay commencement of drug release until the dosage forms reach the ileal region, but then to release most of their drug load when transiting through the ileum and ascending colon. Unlike Crohn's disease, UC affects only the colorectal regions of the GIT, most commonly the rectum and the distal colon. Hence, the development of Entocort and oral Budenofalk has not included their use in UC as the active ingredient does not reach the colon in the therapeutic amounts. Cortiment, on the other hand, has been developed to preferentially deliver budesonide homogenously along the whole colon, with specific application in the treatment of acute mild to moderate UC.

The current standard treatment for induction of remission in mild to moderate active UC is a 5-aminosalicylate (5-ASA) oral preparation (sulfasalazine, mesalazine, balsalazide or olsalazine) with or without a conventional systemic glucocorticosteroid (prednisone or prednisolone).

Proposed dosage regimen

- Adults: The recommended daily dose for induction of remission is one 9 mg tablet in the morning, for up to 8 weeks.
- Paediatric population: The safety and efficacy of Cortiment prolonged release tablets in children aged 0 to 18 years has not yet been established. No data are available; therefore the use in paediatric population is not recommended until further data become available.
- Elderly: No special dose adjustment is recommended. However, experience of the use of Cortiment prolonged release tablets in the elderly is limited.
- Hepatic and renal impairment population: Cortiment was not studied in patients with hepatic and renal impairments; therefore caution should be exercised in the administration and monitoring of the product in these patients.

Regulatory status

The product received initial registration on the ARTG on 31 August 2015.

At the time the TGA considered this application, similar applications had been considered or were under consideration in other countries as detailed in Table 1.

Table 1. Overseas regulatory status.

Procedure	Country	Date of submission	Date of Approval	Proposed indication
	USA (under the name Uceris)	14 Dec 2011	14 Jan 2013	Induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC).
	Netherlands (RMS)	30 May 2011	28 Feb 2013	Induction of remission in adult patients with active, mild to moderate UC, where 5-ASA (5-amino salicylic acid) treatment is not sufficient.
European Union (EU) via Mutual Recognition Procedure (MRP)	Austria	Apr 2014	17 Dec 2014	
	Belgium		26 Nov 2014	
	Bulgaria		Ongoing	
	Croatia		09 Dec 2014	
	Cyprus		Ongoing	
	Czech Republic		14 Jan 2015	
	Estonia		31 Mar 2015	
	Finland		12 Dec 2014	
	Germany		13 January 2015	
	Greece		Ongoing	
	Hungary		19 November 2014	
	Iceland		22 January 2015	
	Ireland		05 December 2014	
	Italy		Ongoing	
	Latvia		27 January 2015	
	Lithuania		23 December 2014	
	Luxembourg		01 April 2015	
	Malta		Ongoing	
	Norway		27 November 2014	
	Poland		23 January 2015	
	Portugal		01 December 2014	
	Romania		19 February 2015	
	Slovakia		19 February 2014	
	Slovenia		18 March 2015	
	Spain		Ongoing	
	Sweden		04 January 2015	
	United Kingdom		19 November 2014	
EU via DCP (submitted in 15 countries)*			Rejected August 2012	Induction of remission in adult patients with active, mild, to moderate UC.
	Canada	April 2015	Ongoing	Induction of remission in adult patients with active, mild, to moderate UC.
	Brazil	05 November 2014	Ongoing	
	Israel	08 April 2014	Ongoing	
	Jordan	23 July 2014	Ongoing	Ulcerative colitis – active
	Kuwait	07 December 2014	Ongoing	

Procedure	Country	Date of submission	Date of Approval	Proposed indication
	Lebanon	28 October 2014	09 April 2015	
	Mexico	September 2014	Ongoing	Induction of remission in adult patients with active, mild to moderate UC.
	RussianFederation	31 July 2014	02 June 2015	Ulcerative colitis – active
	South Africa	10 November 2014	Ongoing	Induction of remission in adult patients with active, mild to moderate UC.
	United Arab Emirates	22 December 2014	ongoing	Ulcerative colitis – active

* Regarding the submission in the European Union (EU), the sponsor stated the following:

'The first application to register Cortiment in the EU sought registration of the product for 'the induction of remission in patients with mild to moderate UC'. This application was reviewed by the Dutch Medicines Evaluation Board under the EMA Decentralised Procedure but initially rejected. This decision was successfully appealed against. Approval in the Netherlands, and subsequently in the other EU member states, was then granted for 'the induction of remission in patients with mild to moderate UC where 5-ASA treatment is not sufficient'. Although the SmPC also notes that some patients may benefit from treatment initially with Cortiment. No trial evidence specifically supporting use of Cortiment in patients where 5- ASA treatment is not sufficient was evaluated as part of the EU application.'

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

The proposed budesonide 9 mg product is formulated as a delayed and prolonged release tablet for oral use, using a multi matrix system technology (MMX) with a mechanism that combines the delayed and extended release properties. It is intended to exert a locally acting anti-inflammatory action by delivering the active directly into the colon.

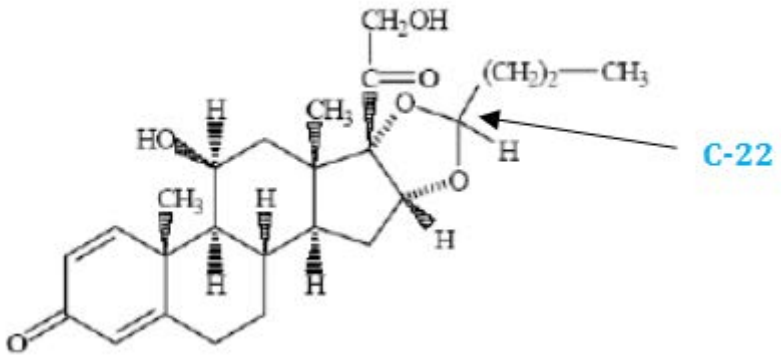
The maximum single dose of the proposed product is 9 mg, and the recommended daily dose of the proposed product is one 9 mg tablet, for up to 8 weeks. One tablet is to be taken orally in the morning, with or without food.

The proposed 9 mg tablet has as a white to off white, round, biconvex, film coated tablet appearance (9.5 mm wide x 4.7 mm thick) with debossing 'MX9' on one side. It is to be packaged in blister packaging, in pack sizes of 10, 20, 30, 50, 60 or 80 tablets.

Drug substance (active ingredient)

Budesonide is a white to almost white crystalline powder and is practically insoluble in water. It contains 9 chiral centres and is a mixture of isomers R and S at Carbon - 22. The content of the S-isomer (epimer A) may vary between 40 to 51%.

Figure 1. Structure of budesonide.



The supplier of drug substance has a Certificate of Suitability showing compliance with the European Pharmacopoeia.

Drug product

The proposed budesonide 9 mg tablets are formulated by Multimatrix System Technology (MMX) as gastro resistant prolonged release tablets.

The excipients are all conventional pharmaceutical ingredients which comply with the Eur. Ph./USP NF monographs.

The formulation of the tablet by MMX applied the following sequences:

- The drug substance budesonide is embedded (totally or partially) in a lipophilic inert matrix (steric acid), which is then surrounded by hydrophilic polymer substance (hydroxypropylcellulose) to create the tablet core.

The core tablet is then covered by the film coating containing the acrylic and methacrylic copolymers, which resist the influence of gastric fluid in the stomach, until it dissolves in the pH environment of greater than 7 (normally found in the terminal ileum).

When the proposed product is administered, the film coat layer protects the tablet until it dissolved in the intestinal fluid of the lower part of the intestine (pH > 7). The intestinal fluid then comes into contact with the hydrophilic matrix polymers, and starts to swell to form a viscous gel matrix, which includes the lipophilic component containing the active. As the fluid penetrates into the gel matrix, the active ingredient is dissolved via diffusion and is released slowly into the GI tract lumen in a controlled manner.

The manufacturing process of the proposed tablets consists of five steps: i) preparation of the wet granulate, ii) drying of the granulate, iii) milling and preparation of the final blend, iv) compression to give the table core, and v) film coating.

The formulation of the tablet as MMX is to provide he delayed extended release to deliver the budesonide directly into the colon and then to slowly disperse the budesonide over a period. The tablet is coated with an acid resistant polymer film which, protects the tablet core during the passage thorough the acidic conditions in the stomach, but which breaks down at or above pH 7.0, in the lower part of the intestine. In the ileum the budesonide is release from the tablet core which contains budesonide combined with specific polymers that provide for the extended release throughout the colon.

The manufacturing process was adequately validated with full production scale batches of the proposed tablets.

The proposed tablet is controlled according to an in-house finished product specification.

- All the issues raised with the finished product Specification (in particular with the tightening of Impurities limits) have been adequately addressed. The revised finished product Specification provided in response to TGA questions is acceptable.
- All the issues which were raised regarding the analytical methods and validation of these methods have been adequately addressed.

The proposed product has been shown to be stable for 36 months stored below 30°C when packaged in the proposed blister pack. The proposed product is not photosensitive.

Biopharmaceutics

Rate and extent of absorption

After oral dosing of plain micronised budesonide, absorption seems to be complete. A large proportion of the unformulated drug is absorbed from the ileum and ascending colon. Systemic availability of budesonide following a single administration of Cortiment prolonged release tablets in healthy volunteers was compared to that of Entocort and the result was similar[1] at about 10%[2], due to first pass metabolism in the liver.

Maximum plasma concentrations of budesonide are approximately 1.3-1.8 ng/mL at 13 to 14 h post administration (see all bio studies below). It has been shown that there is no potential for drug accumulation on repeated dosing (see Study CRO-PK-03-105).

Food effect

Based on results obtained for food effect investigation from Study CRO-PK-03-105, there is a decreasing effect on time after administration of a drug when the maximum plasma concentration is reached (T_{max}), maximum concentration (C_{max}) and Area under the plasma concentration time curve (AUC). This is not considered to have a clinical effect on the efficacy of the product.

Distribution and metabolism

Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85 to 90%. Budesonide undergoes extensive first pass biotransformation in the liver to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Mode, route and rate of elimination

Elimination of budesonide is rate limited by absorption. Budesonide has a high systemic clearance (about 1.2 L/min).

[1] This is based on the recalculated results from Study CRO-PK-06-178. The company's reported results indicate otherwise.
[2] This was not demonstrated directly in any of the studies below. But since the AUC of the proposed product and reference are equivalence, this can be indirectly derived.

The following studies were evaluated

CRO-01-28

Study CRO-01-28 was a single dose, pharmacoscintigraphic and kinetic study of the GI transit and release of a radioactively 152Sm-labelled controlled release formulation of budesonide, in fasting male healthy volunteers. The aim was to demonstrate and quantify the release and absorption of budesonide in the proposed product in the target region (between the ascending and descending colon) by pharmacoscintigraphy and pharmacokinetic (PK) analysis.

Conclusion

The transit time throughout the GI tract and the systemic absorption of the proposed budesonide prolonged release tablets 9 mg demonstrated the following aspects:

1. The tablets arrival in the ascending colon occurred in 7 to 10 hours post dosing.
2. Disintegration or visible erosion of the tablet started in 9.48 hours post dosing, when the tablets were mostly in the ileum, ascending colon and transverse colon.
3. However, the appearance of budesonide in the bloodstream occurred approximately 2 hours earlier, at approximately 6.79 ± 3.24 hours (T_{lag})
4. The budesonide plasma concentration peaked at approximately14.0 hours post dose (T_{max}), which is consistent with that obtained in Study CRO-PK-06-178. The time taken to reach T_{max} from the initial active release from the tablet (T_{max}-T_{lag}) was approximately7.21 hours.
5. The mean C_{max} was 1768.7 ± 1499.8 pg/mL (55.24% coefficient of variation (CV)) and the measured average plasma AUC_{0-24h} was 15607 ± 14549 pg x h/mL (93% CV). Inter subject variability was very high.
6. The percentage of drug absorption during its permanence in the region between the ascending and the descending sigmoid colon accounted for 95.9% of the total systemic budesonide availability.

CRO-PK-03-105

Study CRO-PK-03-105 was a multiple dose pharmacokinetics and food effect study of a new budesonide 9 mg extended release oral formulation in male healthy volunteers. The study objectives were to determine in healthy volunteers the pharmacokinetic profile and the tolerability after single dose in fasted and fed conditions (food effect) and after repeated doses in fasting conditions.

Conclusion

Food affect

There is a food effect on the bioavailability of the proposed budesonide prolonged release tablet 9 mg with regards to the rate and extent of absorption. Food decreased the rate of absorption by approximately 4 hours and lowered the C_{max} by approximately 27%. The extent of absorption decreased slightly by approximately 9% when taken with food immediately prior to dosing. This is not considered to have a clinical effect on the efficacy of the product.

Repeated dose

Budesonide plasma levels did not accumulate after repeated doses. There were statistically significant differences between C_{max} and AUC values between a single dose and repeated doses. C_{max} and AUC decreased by approximately 38% and approximately 40%, respectively, after repeated dosing.

CRO-PK-06-178

Study CRO-PK-06-178 was a bioavailability profile of the MMX budesonide extended release formulation (6 and 9 mg tablets) versus a controlled ileal release formulation, Entocort 3 × 3 mg capsules, in healthy volunteers, under fasting conditions.

Conclusion

- Inter-subject variability was very high among both test formulations and the reference formulation (all > 39.78% CV for C_{max} and Area under the plasma concentration time curve from time 0 to time t (AUC_{0-t})).
- The T_{max} between the proposed product (1 x 9 mg) and the reference product Entocort (3 x 3 mg) are significantly different.
  - The test product reached T_{max} at approximately 12.8 hours, which is approximately 8 hours slower than that of the reference product.
  - This is supportive of the intended mechanism of the proposed product 9 mg, which is to delay the release of the active until it reaches the whole colon sigmoid region of the GI tract, rather than in the terminal ileum and ascending colon region as intended by Entocort.
- Accordingly, the mean C_{max} of the proposed product 9 mg is lower than that of Entocort and the 90% confidence interval (CI) indicates that they are significantly different.
  - Similar to T_{max} above, the lower C_{max} is obtained due to intended drug release mechanism of the proposed tablet in the colon segment of the GI tract.
- The company's conclusion stated the proposed product 9 mg and reference product (3 x 3 mg) are non-equivalent in terms of the extent of absorption of budesonide.However, the evaluator's recalculated values for AUC_{0-t} indicate that the proposed product 9 mg and Entocort are bioequivalent in terms of extent of absorption, indicated by the 90% CI of AUC_{0-t} falling within the 80 to 125% range required to conclude equivalence.

It is noted that all the findings listed in the conclusion above were subjected to the conditions that the sponsor providing additional information in order to comply with the requirements of current EU guideline, as concerns were raised regarding the reference product (Entocort) used in this bioavailability study.The Certificate of Analysis is critical in a bioequivalence study as the Assay content of budesonide in the Test product and Reference product should be within 5% difference in accordance with EU guideline. This determines whether the statistical analysis for C_{max}, AUC would require adjustments for potency difference.

In this case, the Certificate of Analysis for the reference product (Entocort batch #MO0077) was not available from the sponsor, due to the bioequivalence study being conducted prior to the availability of the EU guideline. Therefore, it is not known whether the assay results for the reference product and test product are within 5% difference in accordance with the EU guideline.

The absence of the assay value for the reference product undermined the results obtained for all PK parameters. Hence, an unequivocal conclusion cannot be drawn with regards to the equivalency (or non-equivalency) between the proposed product 9 mg prolonged

release tablet and the reference product Entocort (3 x 3 mg capsule) for Tmax, Cmax and AUC_{0-t}.[3]

An unequivocal conclusion regarding the equivalency (or non equivalency) between the proposed product and reference product with regards to Tmax, Cmax and AUCt could not be drawn.

Quality summary and conclusions

Due to the lack of Certificate of Analysis and therefore, the absence of assay value for the reference product, an unequivocal conclusion cannot be drawn with regards to the equivalency (or non-equivalency) between the proposed product 9 mg prolonged release tablet and the reference product Entocort (3 x 3 mg capsule) with regards to T_{max}, C_{max} and AUC_{0-t}.

Recommendation

Approval for registration of the proposed product can be recommended from a pharmaceutical chemistry perspective.

Approval for registration of the proposed product from a biopharmaceutics perspective cannot be recommended, as an unequivocal conclusion cannot be drawn with regards to the equivalency (or non-equivalence) between the proposed and reference product. However, the proposed product is a locally acting product and the study above is mainly to compare systemic exposure of the proposed product and the reference product.

III. Nonclinical findings

Introduction

Nonclinical pharmacology and toxicology have previously been evaluated by the TGA as part of the registration of other budesonide products. Furthermore, the toxicological profile of budesonide is well documented and there is extensive clinical experience with the medicine, in both respiratory and gastrointestinal disease.

Pharmacology

Primary pharmacology

As the pharmacology of budesonide in relation to IBD is well known, no new pharmacological data were submitted with this application. The data taken from the summary basis of approval (June 2001) for Entocort EC modified release capsules, together with supplementary relevant data from published literature are referenced and discussed.

[3] Sponsor comment: "The trial was in compliance with regulation in force at time of clinical study conduction, before the issuance of current EU guideline. In the Entocort purchased from the market, the assay test specification allows for a variation of NMT 5% to the nominal content of active (3 mg). Furthermore, a sensitivity analysis was performed to evaluate the effect of a deviation of this magnitude on study outcomes. Even by applying ± 5% differences to the reference strength with respect to the theoretical one, these simulations confirmed that rhe product and the reference are not bioequivalent."

Pharmacokinetics

The pharmacokinetics of budesonide has been extensively documented in previous submissions of budesonide containing products (Entocort, Pulmicort, Budamax). No new animal pharmacokinetic studies were submitted with the present Cortiment application.

Toxicology

Single-dose toxicity

Single dose toxicity studies with budesonide have previously been evaluated by the TGA in submissions for previous budesonide containing products (Budenofalk capsules, Entocort capsules, Budenofalk foam).

Repeat dose toxicity

The toxicity profile of budesonide has been previously evaluated in conjunction with submissions to register other dose forms, including products indicated for Crohn's disease and UC, that is, Entocort 3 mg, Budenofalk 3 mg and Budenofalk foam enema 2 mg.

A submitted bridging study conducted in cynomolgus monkeys compared the toxicity of budesonide MMX 9 mg tablet with the reference product Entocort 3 mg capsule. Monkeys (3 of each sex) were given 18 mg once daily, that is, two budesonide MMX 9 mg tablets or six 3 mg Entocort EC capsules, for 28 days. An additional animal of each sex in each group received the same treatment and then maintained for a 14 day recovery period. Both budesonide treatments were well tolerated. There were no toxicological effects or significant intergroup differences in the evaluated study parameters observed in animals receiving the two treatments.

Relative systemic exposure

The repeat dose study in monkeys had complete plasma $AUC_{0-\infty}$ data (measured after 28 days dosing), for males only, as there were insufficient data to enable calculation of mean AUC values for females. The only $AUC_{0-\infty}$ data for a repeat dose study with budesonide MMX in humans was for fasted males (Study CRO-PK-03-105). Where male and female human AUC data were available, it was for single dose studies only. Hence, the human reference value was taken from clinical Study CRO-PK-03-105 (noting that this was for repeat dosing in fasted males only).

Table 2. Exposures in repeat dose toxicity studies.

Species	Study duration	Dose, mg/day (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	AUC0–t# (ng·h/mL)
Monkey% cynomolgus	28 days + 14 days recovery	budesonide MMX (male) 18 (4.7-4.9)	11.79 [9.79]	19.40 [ND]	
		budesonide MMX (female) 18 (6.4-6.7)	21.88 [25.66]	ND [46.03]	
		Entocort EC (male) 18 (4.6-4.9)	28.81 [40.28]	30.26 [41.01]	
		Entocort EC (female) 18 (6.0-6.2)	40.47 [48.13]	40.73 [48.48]	
Human (healthy male volunteers)	7 days	budesonide MMX 9 (0.18 mg/kg/day in a 50 kg person) (MRHD)		9.29 (AUC_{ss}*)	
Human (male + female)	Single dose studies	budesonide MMX 9^ (0.18 mg/kg/day in a 50 kg person) (MRHD)		15.50 - 16.43	13.56 – 15.61
		Entocort EC 9& (0.18 mg/kg/day in a 50 kg person) (MRHD)		14.06	13.39

t varied among studies. % Tabulated AUC values are day 28 values; day 1 values are in [°]. ND, no data. ^ Studies CRO-PK-01-28, CRO-PK-06-178, CRO-PK-03-105. & Study CRO-PK-06-178. Maximum recommended highest dose (MRHD). * Area under the plasma concentration time curve steady state (AUC_{ss})

The monkey data indicate greater budesonide exposure following the Entocort EC treatment, possibly related to lower oral bioavailability with budesonide MMX than with Entocort EC in this species, under these dosing conditions. Thus:

- Mean C_{max} and total exposure (AUC_{0-24h}) for budesonide MMX were about half those for Entocort in females, and less than half in males
- T_{max} budesonide MMX > T_{max} Entocort, therefore a slower rate of absorption for budesonide MMX, in both sexes

- With both budesonide MMX and Entocort, AUC exposures were about 15% lower after repeat dosing compared with a single dose, indicative of lack of accumulation
- In general, females had higher mean peak and total exposures in comparison to males, for both budesonide MMX and Entocort.

Even at up to 18 mg/monkey/day, and allowing for the observation of the higher total exposures in females, the toxicities of budesonide MMX and Entocort were comparable. For both budesonide MMX and Entocort, the systemic exposures (AUC) achieved in the monkey study modestly exceeded the human exposures, for single dose and repeat dose/steady state comparisons.

Unlike cynomolgus monkeys, the human systemic bioavailabilities for both budesonide MMX and Entocort are comparable at about 10%. In humans at both 6 mg/day and at the maximum recommended highest dose (MRHD) (9 mg), it was well tolerated with no evidence of changes in the safety profile of budesonide MMX with increasing dose (Study CB-01-02-02). Although patients receiving budesonide MMX showed a decrease in plasma cortisol concentrations, this is a known glucocorticoid effect and in general the adverse event (AE) profile was consistent with those for other approved budesonide products.

As a further safety assessment, the clinical exposure to budesonide at the MRHD (9 mg) of budesonide MMX (Cortiment) was compared with the known budesonide exposures at the MRHD of other registered budesonide containing oral products (Entocort and Budenofalk capsules), and was found to be comparable.

The results from the monkey study therefore suggest that the use of the budesonide MMX tablet at the proposed MRHD is unlikely to elicit any additional/unexpected systemic toxicities.

Local toxicity considerations

Budesonide begins release from the tablet core of budesonide MMX in the terminal ileum and then continues to be released throughout the colon, so there is the potential for a differing local (GI) tolerance profile with this product compared with other oral budesonide products. Local tolerance was not extensively investigated in the 28 day repeat dose monkey study (dose, 18 mg/day), and there was no placebo control group; however, there was no evidence of local intolerance based on the reported observations ('faecal change' was similar in both budesonide MMX and Entocort groups). The mg/kg doses in the monkey study (4.6 to 6.7 mg/kg/day) were 25 to 37 times the MRHD of 9 mg/day (0.18 mg/kg/day in a 50 kg person); this multiple of the human dose would be somewhat greater with larger patients (for example, 35 to 51 x for 0.13 mg/kg/day in a 70 kg person). The absolute dose of budesonide MMX (and Entocort) administered (18 mg) was 2 x the MRHD. These margins are considered adequate and suggest that the use of Cortiment (budesonide MMX) tablets at the proposed MRHD should be well tolerated. The extensive previous clinical history with oral budesonide products also does not indicate a potential local tolerance issue with this compound.

Taken in conjunction with ratios based on mg/kg weight and consideration of the safety profile of budesonide over many years of clinical practice, it is unlikely that the budesonide MMX will present any new local toxicity concerns. This will be confirmed for the clinical data by the clinical evaluator for the current submission.

Genotoxicity

Budesonide is not considered to possess genotoxic potential, based on published studies with the standard in vitro and in vivo genotoxicity assays, consistent with previous assessments for this compound (published PI documents for Entocort, Pulmicort, Budamax).

Carcinogenicity

No new carcinogenicity study data were submitted; however the sponsor referenced the carcinogenicity studies from the Summary Basis for Approval (SBA), FDA document for Entocort capsules. Several studies, available in the public domain (one published and three in a product monograph for Entocort capsules), have also been previously evaluated by the TGA for earlier submissions, and appropriate statements appear in the PI for Entocort and other registered budesonide products for IBD (Budenofalk capsules, Budenofalk foam).

Reproductive toxicity

The nonclinical reproductive toxicity of budesonide has also been assessed in previous submissions to the TGA for registration of budesonide containing products (refer PI documents for Entocort, Pulmicort, Budamax and Budenofalk). No new data have been provided in the current submission but would be expected to be consistent with the previously assessed reproductive toxicity profile.

Pregnancy classification

The sponsor has proposed pregnancy Category B3.[4] This is consistent with the classifications for other budesonide products for UC and Crohn's disease (Budenofalk Foam, Budenofalk capsules, Entocort capsules), already evaluated and registered.

Paediatric use

Budesonide MMX is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

Summary

A new 28 day oral repeat dose bridging study in cynomolgous monkeys compared Cortiment tablets and Entocort (budesonide) enteric capsules at doses of 18 mg/day (at least 25 x the MRHD on a mg/kg basis). Systemic budesonide exposure following Cortiment was about half that following Entocort, and exceeded clinical systemic exposure at the MRHD. There were no discernible toxicological differences between Cortiment and Entocort treatment groups, and no evidence of local (gastrointestinal) intolerance.

Conclusions and recommendation

There is extensive clinical experience with budesonide through the use of several budesonide containing products, and its clinical efficacy and safety profile are well established. Of particular relevance to the current submission are the registered Entocort capsules and Budenofalk capsules for induction of remission in adults with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon and Budenofalk foam enema for the treatment of active rectal and rectosigmoid disease in ulcerative colitis.

[4] Category B3: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans."

The toxicological bridging study in monkeys did not provide any evidence of a potential for increased systemic glucocorticoid toxicity or local (gastrointestinal) intolerance with Cortiment prolonged release tablets compared with Entocort enteric capsules. The clinical exposure to budesonide at the MRHD of Cortiment is comparable to the known exposures at the MRHD of other registered oral budesonide products.

The nonclinical evaluator also recommended amendments to the draft Product Information document but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

As a synthetic glucocorticoid, budesonide is known to possess anti-inflammatory effects comparable to those of conventional glucocorticoids. There are three budesonide products currently registered on the ARTG for the treatment of IBD, of which two are oral capsules for induction of remission in mild to moderate Crohn's disease affecting the ileum and/or the ascending colon (Entocort and Budenofalk), and one is enema for use in active rectal and rectosigmoid UC (Budenofalk Foam Enema).

Due to extensive absorption from the small intestine and right ascending colon, the currently available oral budesonide formulations are deemed to be unsuitable for the treatment of distal colonic lesions, notably in UC. Using the patented MMX system, the proposed Cortiment prolonged release tablets (also referred to as budesonide MMX) are designed to deliver budesonide at a controlled manner throughout the colon, making it a potential alternative for clinical management of UC. Thus, this product represents a new dosage form of orally administered and topically acting budesonide for a new clinical indication.

Guidance

Contents of the clinical dossier

This application comprises of the following seven clinical studies:

- CRO-01-28; A Phase I pilot pharmaco scintigraphic study in healthy volunteers.[5]
- CRO-PK-03-105; A Phase I study in healthy volunteers, exploring the effects of food on budesonide bioavailability after the administration of a single dose of Cortiment, in addition to characterising pharmacokinetics following 7 consecutive daily doses of Cortiment.[6]
- CRO-PK-06-178; An additional Phase I study in healthy volunteers, comparing budesonide pharmacokinetics following singles doses of Cortiment 6 and 9 mg and Entocort 9 mg (3 x 3 mg) capsules.

[5] Brunner M et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol*. 2006;61:31-38.
[6] D'Haens GR, et al. Clinical trial: Preliminary efficacy and safety study of a new budesonide MMX® 9 mg extended-release tablets in patients with active left-sided ulcerative colitis**.** *J Crohns Colitis*. 2010; 4: 153-160.

- CRO-03-53; A Phase II study in patients with active mild or moderate left-sided UC, evaluating the safety and efficacy of Cortiment.[7]
- CB-01-02/05; A Phase II dose finding study in patients with active mild or moderate UC, comparing the efficacy and safety of 3 and 9 mg OD doses of Cortiment.
- CB-01-02/01 and CB-01-02/02; Two Phase Ill studies, evaluating the efficacy and safety of Cortiment 9 mg.

Of these seven studies, the two Phase III trials (CB-01-02/01 and CB-01-02/02) are pivotal, with the remaining five being supportive.

In addition, this application also contains the following:

- Clinical Overview, Summary of Biopharmaceutical Studies and Associated Analytical Methods, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy and Summary of Clinical Safety.

The sponsor indicated that the dossier submitted in Australia is essentially the same as that submitted in the EU. However, the clinical dataset submitted to the US also contains two additional clinical studies, CB-01-02/04 and CB-01-02/06. The CB-01-02/04 study was a trial for maintenance of remission using a 6 mg once daily dose in inpatients who had already completed the pivotal Phase III studies CB-01-02/01 and CB-01-02/02. This study was conducted to address a specific request by the FDA over concerns with potential use of the product beyond the recommended 8-week regimen. The CB 01 02/06 study was an open label trial with 9 mg treatment, and patients who completed this study were also included in the CB 01 02/04 study.

Paediatric data

The submission did not include paediatric data.

Good Clinical Practice

All studies submitted in the clinical dossier were conducted in accordance to Good Clinical Practice (GCP) standards, except for four sites in the pivotal Phase III Studies CB-01-02/01 and CB-01-02/02, where major GCP violations and efficacy results deemed biologically not plausible were reported during auditing. Consequently, all patients at these four sites were excluded from the intent to treat (ITT) population for efficacy analysis, but remained in the safety population for safety analysis.

Pharmacokinetics

Studies providing pharmacokinetic data

A total of three PK studies were submitted, all were conducted in healthy volunteers (see Table 3 below).

[7] D'Haens GR, et al. Clinical trial: Preliminary efficacy and safety study of a new budesonide MMX 9 mg extended-release tablets in patients with active left-sided ulcerative colitis**.** *J Crohns Colitis*. 2010; 4: 153-160.

Table 3: Submitted pharmacokinetic studies.

Study ref	Objectives	Design	Treatments	Subjects	Results (expressed as mean ± SD)
CRO-01-28	Quantify release and absorption in the colonic region.	Single-dose, single arm, single centre, open study.	^{152}Sm-labelled 9mg controlled release budesonide tablets. Batch 5611.	Healthy male volunteers. N=12. Mean age 35.75 (± 5.12) years.	• Inter-subject variability is high (tablet arrival and leaving times at each gastro-intestinal region of interest varied up to 10-fold among volunteers). • Tablet disintegration started in 9.48 ± 5.11 hours. • Drug plasma levels detected after 6.79 ± 3.24 hours. • C_{max} = 1768.7 ± 1499.8 pg/ml. • AUC_t = 15607 ± 14549 pg.h/ml. • T_{max} = 14.0 ± 7.7 hours. • Approximately 95% of the dose was released in the region of interest.
CRO-PK-06-178	Comparison of bioavailability and PK profiles.	Single-dose, single-centre, open, 3-way cross-over study in fasting conditions.	1 x Budesonide MMX® 9mg tablet, batch MV084. 1 x Budesonide MMX 6mg tablet, batch TV158. 3 x Entocort® EC 3mg capsules, batch MP0077.	Healthy volunteers. N=13 (6 male, 7 female). 1 female subject withdrew and was replaced.	**Plasma budesonide PK parameters (dose-normalised); mean ± SD** MMX® 9mg: C_{max} / dose (pg/ml) 149.9 ± 106.5; AUC_{0-t} / dose (pg.h/ml) 1506.2 ± 868.5; T_{max} (h) 13.3 ± 5.9; $t_{½}$ (h) 8.2 ± 3.7; MRT (h) 21.4 ± 6.8 MMX® 6mg: 193.1 ± 88.7; 1803.0 ± 733.6; 11.4 ± 5.1; 6.6 ± 2.4; 17.0 ± 5.7 Entocort EC: 172.9 ± 37.8; 1488.3 ± 664.8; 4.8 ± 1.4; 7.7 ± 1.8; 11.6 ± 2.7
CRO-PK-03-105	Part 1 Effect of food on bioavailability.	Single-dose, single-centre, open, randomised study.	In each study period: 1 x Budesonide MMX® 9mg tablet. Batch 5706.	Healthy male volunteers. N=12. Mean age 22.3 (± 4.0) years.	**Plasma budesonide PK; mean ± SD** Fasted / Fed C_{max} (pg/ml) 1428.7 ± 1013.5 / 1039.9 ± 601.4 AUC_{0-tl} (pg.h/ml) 14814 ± 11254 / 13486 ± 9368.7 $AUC_{0-\infty}$ (pg.h/ml) 15503 ± 11340 / 14608 ± 9937.9 T_{max} (h) 6. ± 3.4 / 20.7 ± 8.7 T_{lag} (h) 7.4 ± 4.2 / 9.8 ± 3.6 $t_{½}$ (h) 5.4 ± 2.0 / 5.6 ± 2.7 MRT (h) 19.9 ± 4.6 / 24.3 ± 7.1 C_{max} was reached at a later time following administration with food than under fasted conditions (i.e. T_{max} was delayed; p=0.02781). AUC data were also statistically significant (p=0.0078).
	Part 2 Investigation of pharmacokinetics following multiple administration.	Multiple-dose, single-centre, open, randomised study.	1 x Budesonide MMX® 9mg tablet once daily for 7 consecutive days Batch 5706.	Healthy male volunteers. N=12. Mean age 22.3 (± 4.0) years.	• Mean plasma concentration at steady state was 387.3 ± 153.9 pg/ml (Css_{min} 109.9 ± 75.3; Css_{max} 891.3 ± 394.1). • AUCss was 9295.2 ± 3694.2 pg.h/ml. • Tss_{max} was 11 ± 4.9 hours. Mean Css_{min}/C_{max} was 0.87±0.51 (90% CI = 0.16–1.57). AUC_{SS}/AUC_{∞} was 0.82±0.47 (90% CI = 0.16–1.66). Differences in C_{max} and AUC between fed and fasted states were statistically significant in each case. Budesonide does not accumulate upon repeated administration.

Comment: The T_{max} value for Part 1 of Study CRO-PK-03-105 was incorrectly stated as '6. ± 3.4' hours in the clinical summary, while the correct value is 16.0 ± 3.4 h.

None of the PK studies had significant deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

As an established medicinal product, the PK of budesonide has previously been well characterised and documented. No data were submitted in this application on physicochemical characteristics, distribution, metabolism, excretion, PK/PD interaction, or population PK. This is considered acceptable. The absolute bioavailability of the proposed budesonide MMX 9 mg tablet has not been investigated in the submitted clinical studies; however, given that the product is intended to act locally in the lower GIT, the absence of such data is not considered a major deficiency of the application.

The PK data submitted in this application for the proposed prolonged release tablet (budesonide MMX) focus primarily on GIT transit, release and absorption, bioavailability and influence of food and multiple administrations. All studies were conducted in healthy volunteers. No PK study was conducted in the targeted patient population. Given the common clinical presentations (especially diarrhoea) in UC patients, it is likely that the

GIT transit, absorption and bioavailability of the product in the targeted patient population can be significantly different to those in healthy volunteers. It would therefore be more appropriate to have conducted a PK study in UC patients to further characterise the PK profile of the product in the targeted patient population. Nevertheless, the available PK data submitted in this application provided sufficient evidence for the targeted and controlled delivery of budesonide to the lower GIT and supported the proposed once daily dosing regimen.

Pharmacodynamics

Studies providing pharmacodynamic data

No new studies provided.

Dosage selection for the pivotal studies

The dosage of budesonide (9 mg/day) selected for the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) were based on information from the following two sources:

- published literature reporting that single daily oral doses of budesonide 9 mg are more efficacious than multiple daily divided doses in patients with active distal UC[8]
- results from the Phase II dose finding study in patients with mild or moderate active UC, comparing the efficacy and safety of daily doses of the budesonide MMX 3 mg and budesonide MMX 9 mg tablet (CB-01-02/05). In addition, on recommendation by the FDA, the dose of 6 mg/day budesonide was also included in the Phase III studies to try to identify the lowest effective dose for the treatment of patients with active, mild to moderate UC.

Efficacy

Studies providing efficacy data

Two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) were submitted, providing efficacy data for the proposed Cortiment 9 mg prolonged release tablet.

Other efficacy studies

Two Phase II studies (CRO-03-53 and CB-01-02/05) were submitted, providing preliminary efficacy data for the proposed Cortiment 9 mg prolonged release tablet.

For details of these studies please see Attachment 2.

Evaluator's conclusions on efficacy

Efficacy data were generated primarily from the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02), with limited preliminary data also from the two, non-pivotal Phase II studies (CB-01-02/05 and CRO-03-53).

[8] Kolkman JJ et al. Evaluation of oral budesonide in the treatment of active distal ulcerative colitis. Drugs Today (Barc) 2004; 40: 589-601.

In the pivotal studies, almost identical study design was used, with the exception of the concurrent comparator (active control) which was mesalazine (Asacol) in Study CB-01-02/01 and budesonide capsules (Entocort) in Study CB-01-02/02. The dose of mesalazine used in Study CB-01-02/01 was 800 mg three times daily (TDS) (2.4 g/day) which is the dose currently recommended in the US PI for Asacol and within the daily dose range of 2 to 4 g/day (given in 2 divided doses) currently recommended in the Australian Therapeutic Guidelines for induction of remission in mild to moderate active UC. Entocort is not currently registered for the treatment of UC in Australia, EU or USA; thus, the appropriateness of using Entocort as an active efficacy comparator in Study CB-01-02/02 remains questionable.

All patients in the pivotal studies had histological proof of mild or moderate UC prior to entering the studies. The primary efficacy endpoint in both studies was pre-defined clinical remission, which included normalisation of stool frequency, absence of rectal bleeding and improvement of endoscopic score and physician's assessment of Ulcerative Colitis Disease Activity Index (UCDAI). This is considered appropriate and compliant with the current regulatory guidelines.[9] The definition of clinical remission used in these studies was noticeably more rigorous than that described in the clinical trials section of the Australian PI for Budenofalk Foam Enema. Results from both pivotal studies demonstrated that 8 weeks treatment with budesonide MMX 9 mg was associated with a statistically significant improvement in the rate of clinical remission compared to placebo. The placebo rate of remission was 7.4% (95% CI: 2.8-12.1%) in Study CB-01-02/01 and 4.5% (95% CI: 0.2 to 8.8%) in Study CB-01-02/02, both were somewhat lower than the value of 13% (95% CI of 9 to 18%) reported in the published literature.[10] Following 8 weeks of treatment with budesonide MMX 9 mg, the remission rate was 17.9% (95% CI: 11.1 to 24.7%) in CB-01-02/01 and 17.4% (95% CI: 10.3 to 24.6%) in Study CB-01-02/02, both were higher than the placebo values in the studies and also the published literature, suggesting that the proposed product was effective for induction of clinical remission in the targeted patient population.

Supportive evidence was also observed in some of the other efficacy endpoints (most noticeably symptom resolution and less so histological healing), especially in Study CB-01-02/02. Nevertheless, no significant change in the secondary efficacy endpoints (clinical improvement and endoscopic improvement) was apparent in either of the pivotal studies following treatment with budesonide MMX 9 mg, casting some doubt on the actual clinical benefits of the proposed product. In both studies, clinical improvement was linked with endoscopic improvement which was part of the UCDAI used for the measurement of clinical improvement. It is therefore possible that the lack of clinical improvement in these studies may have at least in part, reflected disagreements and/or variations in endoscopic evaluation especially of proximal colonic lesions, leading to underestimates of changes in the patients (especially those with extensive pancolonic lesions). Due to differences in patient population, definition of primary endpoint and other study conditions it is obviously inappropriate to directly compare the efficacy results in the studies of budesonide MMX 9 mg with those of the currently approved topical budesonide (Budenofalk Foam Enema).

With regards to the non-pivotal studies, there were some significant shortcomings in the design and conduct of these studies. In Study CRO-03-53, patients with only left sided UC were recruited. In Study CB-01-02/05 histological proof of UC was not required for

[9] CHMP/EWP/18463/2006; Guideline on the development of new medicinal products for the treatment of ulcerative colitis

[10] Su C, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology*. 2007;132 :516-626.

patients entering the study which may, at least in part attribute to its substantially higher remission rates than in other studies. The current regulatory guideline requires that '*only patients having confirmed ulcerative colitis should be included in trials'*. Caution should therefore be exercised when interpreting the potential clinical relevance of the preliminary efficacy results in the non-pivotal studies.

Safety

Studies providing safety data

Safety data in UC patients were mainly generated from the two pivotal efficacy studies (CB-01-02/01 and CB-01-02/02), with additional safety data also provided in the two preliminary efficacy studies (CRO-03-53 and CB-01-02/05). In addition, limited safety data in healthy volunteers were collected in the three PK studies (CRO-01-28, CRO-PK-03-105 and CRO-PK-06-178).

Safety assessments were conducted by evaluation of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), deaths and discontinuations due to TEAEs, clinical laboratory tests (including cortisol concentrations and adrenocorticotropic hormone (ACTH) stimulation tests), glucocorticoid effects, physical examinations and vital signs.

Patient exposure

A total of 613 subjects received as least one dose of budesonide MMX treatment, with 36 as healthy volunteers and 577 as UC patients. In the 36 healthy volunteers, there were a total of 48 single dose episodes, with 12 episodes at the dose of 6 mg and 36 episodes at the dose of 9 mg. In addition, of the 36 healthy volunteers, 12 received multiple daily doses of 9 mg for 7 days. Of the 577 patients with mild or moderate active UC, 509 were exposed to budesonide MMX at daily dose of either 6 mg (n = 254) or 9 mg (n = 255) for up to 56 days in the two pivotal efficacy studies. The remaining 68 UC patients were exposed to daily doses of budesonide MMX at either 3 mg (n = 17) for up to 56 days, or at 9 mg for up to 28 days (n = 18) or 56 days (n = 33) in the two preliminary efficacy studies. A summary of the patient exposure data is shown in Table 4.

Table 4: Exposure to budesonide MMX in clinical studies according to dose and duration.-+

Budesonide MMX	Subjects	Duration			
		1 day	7 days	28 days	56 days[#]
3 mg	Health volunteers				
	UC patients				17
6 mg	Health volunteers	12			
	UC patients				254
9 mg	Health volunteers	36	12		
	UC patients			18	288

[#] Not all UC patients completed the scheduled 8 weeks of treatment.

Safety issues with the potential for major regulatory impact

Morning plasma cortisol

Pivotal studies

Morning plasma cortisol levels at baseline and changes from baseline by visit in studies CB-01-02/01 and CB-01-02/02 were summarised. There were large inter subject variations in the data (evident by large standard deviation (SD) values). Overall, dose dependent decreases from baseline in mean morning plasma cortisol levels were noted in the budesonide MMX 6 mg and 9 mg groups at all study visits. The mean decreases ranged from 52.9 to 91.2 nmol/L in the budesonide MMX 6 mg group, and 98.6 to 175.7 nmol/L in the budesonide MMX 9 mg group of Study CB-01-02/01, and from 48.3 to 89.2 nmol/L in the budesonide MMX 6 mg group, and 103.3 to 150.1 nmol/L in the budesonide MMX 9 mg group of Study CB-01-02/02. The decreases did not appear to be time dependent, as the mean decreases at Visit 5/Final Visit were not greater than at the earlier visits (Visits 3 and 4). The reported decrease in morning cortisol also did not appear to be associated with an increase in clinical glucocorticoid effects.

Other studies

Morning plasma cortisol levels were also determined in the two non-pivotal Phase II Studies CRO-03-53 and CB-01-02/05.

Data for Study CRO-03-53 were summarised. Treatment with budesonide MMX 9 mg was associated with a decrease in morning plasma cortisol, more pronounced after 8 weeks of treatment than after 4 weeks of treatment. After adrenocorticotropic hormone (ACTH) stimulation in the short Synacthen test during the final visit at Week 8, normal response in hypothalamus pituitary adrenal (HPA) axis function was detected in 9 out of 15 (60%) patients treated with budesonide MMX 9 mg for the last 4 weeks, but only in 6 out of 14 (43%) patients treated with budesonide MMX 9 mg for 8 weeks, indicating suppression of the HPA axis following treatment with the product.

Data for study CB-01-02/05 are summarised in Table 5. Decreases in mean morning plasma cortisol levels were apparent in the budesonide MMX 9 mg group, seemingly more marked following 8 weeks of treatment (by -154.2 nmol/L at Visit 2) than following 4 weeks of treatment (by -133.5 nmol/L at Visit 1). Two patients [information redacted] treated with budesonide MMX 9 mg were reported with 'clinically relevant abnormal' values at Visit 1, with morning plasma cortisol in subject [information redacted] falling from 875.9 nmol/L at screening to 23.06 nmol/L at Visit 1 (a decrease of 97.4%), and that in subject [information redacted] from 614.0 nmol/L at screening to 6.98 nmol/L at visit 1 (a decrease of 98.9%). It was concluded by the investigator that treatment with budesonide MMX at 9 mg, but not at 3 mg, was associated with a moderate inhibition of cortisol production.

Table 5: Morning plasma cortisol (nmol/L) at baseline screening and changes from baseline screening by visit in study CB-01-02/05.

		budesonide-MMX 3 mg	budesonide-MMX 9 mg	Placebo
Screening visit	N	17	15	17
	Mean	458.77	507.82	424.30
	SD	219.43	155.89	170.93
	Median	377.50	445.10	387.00
	Min, Max	221.18, 1088.0	255.95, 875.90	198.00, 919.70
Change from Screening at Visit 0 (day 0)	N	17	15	17
	Mean	-31.94	-19.99	-79.09
	SD	188.74	188.72	168.98
	Median	30.34	-4.60	-54.00
	Min, Max	-707.5, 108.30	-467.0, 332.10	-588.9, 170.90
Change from Screening at Visit 1 (day 28±2)	N	17	13	15
	Mean	-83.86	-133.5	-78.10
	SD	232.87	363.16	213.20
	Median	-53.60	-97.20	-68.20
	Min, Max	-730.80, 312.10	-852.80, 594.80	-679.60, 232.90
Change from Screening at Visit 2 (day 56 ± 2)	N	15	14	16
	Mean	11.03	-154.2	-7.19
	SD	195.47	264.47	227.09
	Median	22.90	-113.7	17.71
	Min, Max	-368.00, 320.00	-589.00, 186.30	-604.10, 497.00
NB: Normal reference range for morning cortisol not specified in the study				

For further details of the safety evaluation please see Attachment 2.

Post marketing data

One periodic safety update report (PSUR) for the period of 14 January to 30 April 2013 was submitted. This is the first PSUR on budesonide MMX since the product was first authorised as Uceris in the USA on 14 January 2013 and as Cortiment in Netherlands on 28 February 2013. This report requires evaluation by the TGA.

Evaluator's conclusions on safety

As an established glucocorticoid, the pharmacological and toxicological profile of budesonide has previously been well characterised and documented. With regard to the clinical safety profile of the proposed budesonide MMX 9 mg tablet, relevant data from the pivotal Phase III and non-pivotal Phase II studies showed that the product was safe and generally well tolerated by patients with mild to moderate active UC. The incidences and severity of AEs, TEAEs and SAEs were generally similar across all treatment groups in these studies. No deaths have been reported and the reported SAEs were consistent with the events that would be expected in the targeted patient population with a relapsing and remitting disease. The overall safety profile of the product was generally comparable with that of Entocort which was used as an active comparator in Study CB-01-02/02.

Clinically, one of the main concerns over long term systemic use of a glucocorticoid is the potential for glucocorticoid effects and for suppression of the HPA axis. Indeed, data provided in the clinical studies showed that budesonide MMX treatment was associated with dose dependent decreases in morning plasma cortisol levels. Results of the short Synacthen test in Study CRO-03-53 also showed evidence of inhibitory effects on the HPA axis following treatment with budesonide MMX 9 mg. Nevertheless, no unequivocal evidence of glucocorticoid effects was apparent clinically in the submitted studies. Long term systemic use of glucocorticoids is known to potentially cause osteoporosis. No clinical data were provided by the sponsor for the potential adverse effects of budesonide MMX on bone mineral density. However, given that the product is proposed for use of up to only 8 weeks for induction of remission, the absence of such data is not considered a major deficiency of this application.

Overall, the clinical safety profile of the proposed budesonide MMX 9 mg tablet is considered to have been adequately characterised and similar to the known profile of oral budesonide. No new safety issue was identified from analysis of the submitted clinical safety data. However, it should be noted that safety assessment of the product was conducted only during the intended 8 week period of clinical use. Thus, the actual clinical safety of the product beyond the intended 8 week regimen remains largely unknown. It would therefore be prudent to consider limiting the clinical use of this product for up to 8 weeks, thereafter all patients should cease the treatment regardless of being responsive to the treatment or not. This consideration is also consistent with the current Therapeutic Guidelines which state that corticosteroids do not prevent relapse of UC and have unacceptable long term adverse effects.

First round benefit-risk assessment

First round assessment of benefits

The current standard of treatment for induction of remission in mild to moderate active UC is a 5-aminosalicylate oral preparation (sulfasalazine, mesalazine, balsalazide or olsalazine) with or without a conventional systemic glucocorticosteroid (prednisone or prednisolone). Budesonide is an established synthetic glucocorticosteroid, with anti-inflammatory effects comparable to those of conventional glucocorticoids. There are three budesonide containing products currently registered in Australia for the treatment of IBD,

two of which are delayed release oral formulations (Entocort modified release capsules and Budenofalk Enteric capsules) for the induction of remission in mild to moderate Crohn's disease and the other is a topical product (Budenofalk Foam Enema) for use in active rectal and rectosigmoid UC. The proposed budesonide MMX 9 mg tablet (Cortiment) represents a new formulation of orally administered and topically acting budesonide for the induction of remission in mild to moderate active UC. Given that no oral budesonide formulation is currently available for the treatment of UC and the currently registered Budenofalk Enema is suitable only for patients with left sided disease, the proposed Cortiment tablet offers the potential benefit as an alternative option for the proposed indication, especially in patients with proximal involvement of the disease (for example, pancolitis). The intended once daily dosing regimen for the product also offers a convenient method of treatment and hence potentially assists in better compliance.

First round assessment of risks

The overall safety profile of the proposed Cortiment tablet following the intended clinical use of 8 weeks has been found to be generally comparable with that of Entocort, another controlled release oral budesonide formulation currently registered in Australia for the treatment of Crohn's disease. Cross study comparison on the safety profile of the product is generally not considered appropriate due to the fact that the clinical studies were conducted under different conditions.

Evidence for suppression of the HPA axis was observed, although no unequivocal evidence for glucocorticoid effects was apparent clinically in the submitted studies. The absence of unequivocal evidence for clinically noticeable glucocorticoid effects is not unexpected given the relatively short duration of the clinical studies. The safety profile of Cortiment following a longer period of clinical use has not been investigated in the submitted clinical studies. Thus, the actual clinical safety of the product beyond the intended 8 week regimen remains largely unknown. In other words, from a regulatory view point, the potential risks of the product associated with its possible off label use (for example, for prolonged treatment in maintenance of remission) represent a safety concern, especially given that corticosteroids are deemed to have no role in maintenance therapy as they do not prevent relapse of UC and have unacceptable long term adverse effects (Therapeutic Guidelines, Gastrointestinal).

First round assessment of benefit-risk balance

The benefit-risk balance of the proposed Cortiment tablet, given its intended clinical usage, is considered favourable, as it offers a convenient alternative for the proposed clinical indication with an overall safety profile similar to that of other oral budesonide.

First round recommendation regarding authorisation

There is no clinical objection to registration of the proposed Cortiment tablet for use of up to 8 weeks for induction of remission in patients with mild to moderate active UC.

Clinical questions

No specific clinical question is raised to the sponsor in the First round clinical evaluation report. However, it is noted that long term safety and efficacy data were made available to

the FDA but were not included in this submission. A summary of the maintenance Study CB-01-02/04 should therefore be requested for consideration.[11]

Second round evaluation of clinical data submitted in response to questions

No separate Second round clinical evaluation was performed.

Second round benefit-risk assessment

No separate Second round clinical evaluation was performed.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Method of administration

One tablet of Cortiment is taken orally in the morning, with or without food. The tablet should be swallowed with a glass of water and must not be broken, crushed or chewed as the film coating is intended to ensure prolonged release.

Quality

Approval for registration of the proposed product can be recommended from a pharmaceutical chemistry perspective.

However, approval for registration of the proposed product *cannot* be recommended from a biopharmaceutics perspective. In particular, there is a lack of unequivocal conclusion [in terms of the rate and extent of absorption of the proposed test product Cortiment (1 x 9 mg prolonged release tablet) in comparison with the reference product Entocort (3 x 3 mg capsule) in Study CRO-PK-06-178.

However, whether this lack of unequivocal conclusion has a significant effect on the efficacy and safety profile of the proposed product will be a decision of the clinical Delegate.

Nonclinical

There were no objections on nonclinical grounds to the registration of Cortiment (budesonide MMX) tablets for the proposed indication.

[11] The sponsor provided a copy of Study CB-01-02/04 to the TGA.

Clinical

The clinical evaluator identified three studies (one study has Parts 1 and 2) with PK data, and three studies on efficacy and safety which could be taken as a total of seven studies altogether.

Studies with Pharmacokinetic data:

- CRO-01-28; a Phase I pilot pharmaco scintigraphic study in healthy volunteers
- CRO-PK-03-105; a Phase I study in healthy volunteers, exploring the effects of food on budesonide bioavailability after the administration of a single dose of Cortiment, in addition to characterising pharmacokinetics following 7 consecutive daily doses of Cortiment
- CRO-PK-06-178; An additional Phase I study in healthy volunteers, comparing budesonide pharmacokinetics following singles doses of Cortiment 6 mg and 9 mg and Entocort 9 mg (3 x 3 mg) capsules (CRO-PK-06-178)

The clinical evaluator made the following overall conclusions on pharmacokinetics:

- As an established medicinal product, the PK of budesonide has previously been well characterised and documented. No data were submitted in this application on physicochemical characteristics, distribution, metabolism, excretion, PK/PD interaction, or population PK. This is considered acceptable
- The absolute bioavailability of the proposed budesonide MMX 9 mg tablet has not been investigated in the submitted clinical studies; however given that the product is intended to act locally in the lower GIT the absence of such data is not considered a major deficiency of the application
- The PK data submitted in this application for the proposed prolonged release tablet (budesonide MMX) focus primarily on GIT transit, release and absorption, bioavailability and influence of food and multiple administrations. All studies were conducted in healthy volunteers. No PK study was conducted in the targeted patient population. Given the common clinical presentations (especially diarrhoea) in UC patients, it is likely that the GIT transit, absorption and bioavailability of the product in the targeted patient population can be significantly different to those in healthy volunteers. It would therefore be more appropriate to have conducted a PK study in the UC patients to further characterise the PK profile of the product in the targeted patient population. Nevertheless, the available PK data submitted in this application provided sufficient evidence for the targeted and controlled delivery of budesonide to the lower GIT, and supported the proposed once daily dosing regimen.

Studies with efficacy data

Pivotal efficacy/safety studies

Study CB-01-01/01

This was a multi-centre, randomised, double blind, double dummy, parallel group comparative study in patients with mild or moderate active UC. The study compared the efficacy and safety of budesonide MMX 6 mg and 9 mg tablets with placebo and, also compared Asacol 6 x 400 mg over encapsulated tablets with placebo in four treatment groups over an 8 week treatment period. The Asacol over encapsulated tablet is an USA registered product containing 400 mg mesalazine (also known as mesalamine a United States Adopted Name (USAN)). Eligible patients underwent a wash out period of 2 days, prior to being randomised to one of the following four treatment groups:

- Group 1 (budesonide MMX 6 mg); One budesonide MMX 6 mg tablet, in the morning (mane); and two placebo Asacol tablets, TDS
- Group 2 (budesonide MMX 9 mg); One budesonide MMX 9 mg tablet, mane; and two placebo Asacol tablets, TDS
- Group 3 (Placebo) One placebo budesonide MMX tablet, mane; and two placebo Asacol tablets, TDS
- Group 4 (Asacol) One placebo budesonide MMX tablet, mane; and two Asacol 400 mg tablets, TDS.

During the study, five visits to the study centre were scheduled: one at screening and four in the double blind treatment period (Day 1, and Weeks 2, 4 and 8). A safety follow up visit took place about 2 weeks after the final study visit.

The primary objective was to evaluate the efficacy and safety of budesonide MMX 6 mg and 9 mg oral tablets when compared to placebo for the induction of remission in patients with mild or moderate active UC, when administered for 8 weeks.

The secondary objective was to evaluate the clinical improvement and endoscopic improvement after 8 weeks treatment with budesonide MMX 6 mg and 9 mg oral tablets when compared to placebo in patients with mild or moderate active UC.

Other objectives were to evaluate symptom resolution and histological healing after 8 weeks of treatment with budesonide MMX, the improvement in clinical and bio humoral parameters and in the Inflammatory Bowel Disease Quality of Life (IBD QoL) questionnaire after 8 weeks of treatment with budesonide MMX, and the efficacy and safety of Asacol over encapsulated tablets (2 x 400 mg TDS) when administered for 8 weeks in patients with mild or moderate active UC.

The primary efficacy end point was the percentage of patients with clinical remission after 8 weeks of treatment. Clinical remission was defined as a UCDAI score of ≤ 1, with all of the following:

- A score of 0 for rectal bleeding and stool frequency (assessed from the patient diary)
- A normal mucosa (no evidence of mucosal friability as determined by endoscopy)
- A ≤ 1point reduction in the endoscopy score from baseline to Visit 5/Final Visit.

The secondary efficacy endpoints were:

- Clinical improvement, defined as a ≥ 3 point improvement in UCDAI score from baseline to Visit 5/Week 8
- Endoscopic improvement, defined as ≥ 1 point improvement in the mucosal appearance sub score of the UCDAI from baseline to Visit 5/Week 8.

The other efficacy end points included the following:

- Symptom resolution, defined as having score of 0 for both rectal bleeding and stool frequency from the UCDAI at Visit 5/Week 8
- Histological healing, defined as total histological assessment score of ≤ 1 on all biopsy specimens at Visit 5/Week 8, according to Saverymuttu[12]

[12] Saverymuttu SH et al. Indium 111-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. A comparison with colonoscopy, histology, and fecal indium 111-granulocyte excretion. *Gastroenterology*.1986;90:1121-1128.

- Proportion of patients with a Clinical Activity Index (CAI) score ≤ 4 at Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 8
- Treatment failure, defined as worsening of UC, requiring specific medical treatment; the proportion of patients who discontinued from the study due treatment failure at Visit 3/Week 2, Visit 4/Week 4, and Visit5/Week 8
- Change in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 8
- Change in the IBD QoL questionnaire at Visit 3/Week 2, Visit 4/Week 4, and Visit 5/Week 8.

For efficacy endpoint analysis, the level of statistical significance was set at $p \leq 0.025$ for budesonide MMX 6 mg and 9 mg groups versus placebo, and at $p \leq 0.05$ for all other comparisons. Initially, 492 patients (123 per group) were planned for randomisation to ensure evaluation of 440 patients (110 per group). Subsequently, a total of 803 patients were screened, of whom 510 were randomised, but only 349 completed the study.

Primary efficacy outcome according to the clinical evaluator:

- As shown in Table 6 and Table 7 a statistically significant difference in the percentage of patients with clinical remission after 8 weeks of treatment was noted for the budesonide MMX 9 mg group compared to placebo group, in both the intent to treat (ITT) ($p = 0.0143$) and per protocol (PP) ($p = 0.0027$) populations.

Table 6. Study CB-01-01/01. Remission rates for the ITT population after 8 weeks.

ITT population	Placebo N=121	MMX 9 mg N=123	MMX 6 mg N=121	Asacol[ł] N=124
Remission: n (%)	9 (7.4)	22 (17.9)	16 (13.2)	15 (12.1)
95% CI	2.8, 12.1	11.1, 24.7	7.2, 19.3	6.4, 17.8
Difference between active and placebo:		10.4	5.8	4.7
95% CI		2.2, 18.7	-1.8, 13.4	-2.7, 12.1
p-value		0.0143	0.1393	0.2200

ł Not powered to show statistical significance versus the budesonide MMX groups.

Table 7. Study CB-01-01/01. Remission rates for the PP population after 8 weeks.

PP population	Placebo N=61	MMX 9 mg N=69	MMX 6 mg N=72	Asacol ǂ N=73
Remission: n (%)	5 (8.2)	20 (29.0)	11 (15.30)	10 (13.7)
95% CI for remission rate (%)	1.3, 15.1	18.3, 39.7	7.0, 23.6	5.8, 21.6
Difference between active and placebo:		20.8	7.1	5.5
95%CI		8.1, 33.5	-3.7, 17.9	-5.0, 16.0
p-value		0.0027*	0.2110	0.3144

ǂ Not powered to show statistical significance versus the budesonide MMX groups.

- Subgroup analysis of remission by gender, age and geographic region revealed that females appeared to respond better than males, patients in the great median age subgroup appeared to respond better than others, and India showed greater remission rates than patients from other countries.

Secondary and other efficacy outcomes as per the CE:

- With the exception of symptom resolution, the differences between the treatment and placebo groups regarding both the secondary and other efficacy endpoints were not statistically significant.
- For symptom resolution, the changes in both budesonide MMX 9 mg and 6 mg groups when compared with the placebo group, reached statistical significance in worse case analysis (p = 0.0258 and 0.0214 respectively). Nevertheless, analysis of the observed case data did not demonstrate a statistically significant difference between the placebo and any of the treatment groups (44.9%, 43.2% and 36.0% in the budesonide MMX 9 mg, budesonide MMX 6 mg and Asacol groups, respectively versus placebo 29.9%) with respective p values of 0.0631, 0.0941 and 0.4199 for the three treatment groups.
- In case of histological healing, the percentage of patients with this endpoint parameter was less in the budesonide MMX 9 mg (4.1%) compared with the placebo (6.6%) group, although the difference was not statistically significant.
- Overall, while somewhat supportive, results for the secondary and other efficacy endpoints did not appear to be very convincing.

Study CB-01-02/02

This multi-centre study was of randomised, double blind, double dummy, parallel group comparative design in patients with mild or moderate active UC. The study compared the budesonide MMX 6 mg and 9 mg tablets to placebo and also compared Entocort 3 x 3 mg capsules (9 mg) to placebo over an 8 week treatment period. Eligible patients underwent a wash out period of 2 days, prior to being randomised to one of the following treatment groups:

- Group 1 (Budesonide MMX 6 mg): One budesonide MMX 6 mg tablet plus three placebo Entocort capsules, mane
- Group 2 (Budesonide MMX 9 mg): One budesonide MMX 9 mg tablet plus three placebo Entocort capsules, mane

- Group 3 (Entocort 9 mg): Three Entocort 3 mg capsules plus one placebo budesonide MMX tablet, mane
- Group 4 (Placebo): One placebo budesonide MMX tablet plus three placebo Entocort capsules, mane

Study visits were as for Study CB-01-02/01.

The primary objective was to evaluate the efficacy and safety of budesonide MMX 6 mg and 9 mg oral tablets when compared to placebo in patients with mild or moderate active UC, when administered for 8 weeks.

The secondary objective was to evaluate the clinical improvement and endoscopic improvement after 8 weeks treatment with budesonide MMX 6 mg and 9 mg oral tablets when compared to placebo in patients with mild or moderate active UC.

Other objectives were to evaluate symptom resolution and histologic healing after 8 weeks of treatment with budesonide MMX, the improvement in clinical and bio humoral parameters and in the IBD QoL questionnaire after 8 weeks of treatment with budesonide MMX, and the efficacy and safety of Entocort capsules (3 x 3 mg/day) when administered for 8 weeks in patients with mild or moderate active UC.

The primary, secondary and other efficacy end points of this study were identical to those of Study CB-01-01/01.

For efficacy end point analysis, the level of statistical significance was set at $p \leq 0.025$ for the budesonide MMX 6 mg and 9 mg groups versus placebo and at $p \leq 0.05$for all other comparisons. Initially, 492 patients (123 per group) were planned for randomisation to ensure evaluation of 440 patients (110 per group). Subsequently, a total of 613 patients were screened, of whom 512 were randomised, but only 272 completed the study.

Primary efficacy outcome according to the clinical evaluation

As per Tables 8 and 9 below, data on the percentage of patients with clinical remission after 8 weeks of treatment revealed a statistically significant difference ($p = 0.0047$) between budesonide MMX 9 mg group and the placebo group in both the ITT and PP populations. A statistically significant difference was also noted for the Entocort 9 mg group compared to the placebo group, although the difference was less marked than the budesonide MMX 9 mg group (8.1% versus 12.9% in the ITT, 10.7% versus 16.6% in PP population).

Table 8. Study CB-01-02/02: Patients with clinical remission after 8 weeks of treatment in the ITT population.

ITT population	Placebo N=89	MMX 9 mg N=109	MMX 6 mg N=109	Entocort[ł] N=103
Remission: n (%)	4 (4.5)	19 (17.4)	9 (8.3)	13 (12.6)
95% CI	0.2, 8.8	10.3, 24.6	3.1, 13.4	6.2, 19.0
Difference between active and placebo:		12.9	3.8	8.1
95 % CI		4.6, 21.3	-3.0, 10.5	-0.4, 15.9
p-value		0.0047*	0.2876	0.0481*

ł Not powered to show statistical significance vs. the budesonide –MMX groups.

Table 9. Study CB-01-02/02: Patients with clinical remission after 8 weeks of treatment in the PP population.

PP population	Placebo N=67	MMX 9 mg N=84	MMX 6 mg N=73	Entocortł N=72
Remission: n (%)	4(6.0)	19 (22.6)	8 (11.0)	12 (16.7)
95% CI	0.3, 11.6	13.7, 31.6	3.8, 18.1	8.1, 25.3
Difference between active and placebo		16.6	5.0	10.7
95%		6.1, 27.2	-4.2, 14.1	0.4, 21.0
p-value		0.0047*	0.2922	0.0483#

ł Not powered to show statistical significance vs. the budesonide –MMX groups.

Subgroup analysis of remission by gender, age and geographic region revealed that males appeared to respond better than females, patients in the less than median age subgroup appeared to respond better than others, and patients from Russia and Eastern Europe showed greater remission rates than patients from other countries.

Overall, the findings in the subgroup analysis were inconsistent with those in Study CB-01-02/01.

Secondary and other efficacy outcomes as per the clinical evaluation

With the exemption of symptom resolution, the differences between the treatment and placebo groups regarding both the secondary and other efficacy endpoints were not statistically significant.

For symptom resolution, a statistically significant difference was noted in the budesonide MMX 9 mg group (23.9%) when compared to the placebo group (11.2%) in worse case analysis ($p = 0.0220$). A similar statistically significant difference in symptom resolution was also noted between the budesonide MMX 9 mg group (36.1%) and the placebo group (17.5%) in observed case analysis ($p = 0.0196$; data not presented in the table above).

In the case of histological healing, there appeared to be a clinical meaningful improvement in the budesonide MMX 9 mg group (16.5%) compared to the placebo group (6.7%) in worse case analysis, although the difference (9.8%) was not statistically significant ($p = 0.00361$). In observed case analysis for histological healing, a similar improvement was also noted in the budesonide MMX 9 mg group compared with the placebo group (25.4% versus 10.3%, $p = 0.0293$), although the difference (15.0%) did not reach the study protocol predefined statistical significance level at $p \leq 0.025$.

Overall, results for the secondary and other efficacy endpoints in this study appeared to be more supportive and convincing than those in Study CB-01-02/01.

Other efficacy studies

Study CRO-03-53

This was a multi-centre, randomised, 2 period, placebo controlled study, with 4 weeks of blinded treatment (Period 1) followed by 4 weeks of open label extension (Period 2). The main objective of the study was to assess whether the budesonide MMX 9 mg tablet was able to induce a clinical improvement in patients with mild to moderate active left sided UC.

A total of 21 male and 15 female patients, aged 18 to 65, with left sided UC and a clinical activity index (CAI) < 14, were randomised to the placebo and budesonide MMX 9 mg groups. Of the 36 patients, only 32 were evaluable (ITT population), and the other 4 were excluded due to protocol violations. During Period 1, the patients were treated daily with either budesonide MMX 9 mg or matched placebo for 4 weeks. During Period 2, all patients in both groups were treated daily with budesonide MMX 9 mg for a further 4 weeks.

The primary efficacy endpoint was the number of patients achieving a reduction by at least 50% of baseline CAI or remission (CAI ≤ 4) after 4 weeks of treatment with budesonide MMX 9 mg or placebo.

The secondary efficacy endpoints were the number of patients achieving a reduction by at least 70% of baseline CAI or remission (CAI ≤ 4) after 8 weeks, endoscopic improvement in rectal biopsies, and changes in CRP levels at Weeks 4 and 8.

The preliminary efficacy outcome as per the clinical evaluation

Overall, there appeared to be a greater number of patients achieving a response to budesonide MMX 9 mg treatment in the efficacy parameters. However, the differences between the two study groups were not statistically significant.

In terms of changes from baseline, the budesonide MMX 9 mg group showed clinically meaningful CAI and endoscopic improvements following 8 weeks of treatment, but generally not after 4 weeks of treatment, suggesting that treatment for 8 weeks was necessary for a meaningful therapeutic benefit of the product.

Study CB-01-02/05

This was a multi-centre, randomised, double blind, placebo controlled study. The objective of the study was to evaluate the dose response of budesonide MMX 3 mg and 9 mg oral tablets compared to placebo in patients with mild or moderate active UC when administered for 8 weeks.

A total of 24 male and 25 female patients, aged 18 to 75, with a UCDAI ≥ 4 and ≤ 10, were randomised to the placebo, budesonide MMX 9 mg, and budesonide MMX 3 mg groups. Of the 49 patients, 37 had at least one post baseline evaluation completed and were included in the ITT efficacy analyses, but only 35 completed the study as per protocol. Treatment was given once a day for 8 weeks. All patients received a wash out period of 2 days prior to the commencement of treatment. Histological proof of UC at study entry was not a stated requirement in the study protocol.

The primary efficacy endpoint was the percentage of patients achieving UCDAI remission at Week 8. UCDAI remission was defined as a UCDAI score ≤ 1 with a score of 0 for rectal bleeding and stool frequency, and ≥ 1 point reduction from baseline in the endoscopy score.

The secondary efficacy endpoints were: percentage of patients with score 0 for blood in stools and stool frequency after 4 and 8 weeks of treatment; percentage of patients with CAI ≤ 4 after 4 and 8 weeks of treatment; percentage of patients with endoscopic healing (score 0) after 8 weeks of treatment; degree of CAI improvement after 4 and 8 weeks of treatment; and degree of UCDAI improvement after 8 weeks of treatment.

The preliminary efficacy outcome as per the clinical evaluation

A greater proportion of patients with a clinically meaningful improvement in most of the efficacy endpoints were noted in the budesonide MMX 9 mg group, compared to the placebo and budesonide MMX 3 mg group.

As with the other preliminary Phase II Study CRO-03-53, a greater CAI improvement was apparent following 8 weeks of treatment compared to 4 weeks of treatment.

It is noteworthy that due to the small group size, a statistical analysis was not conducted for the efficacy results, and thus the level of statistical significance in the differences between the study groups remains largely unknown.

On the overall efficacy, the clinical evaluator made the following conclusions

- Efficacy data were generated primarily from the two pivotal Phase III Studies (CB-01-02/01 and CB-01-02/02) with limited preliminary data also from the two non-pivotal Phases II Studies (CB-01-02/05 and CRO-03-53). The appropriateness of using Entocort as an active efficacy comparator in Study CB-01-02/02 is questionable.
- Results from both pivotal studies demonstrated that 8 weeks treatment with budesonide MMX 9 mg was associated with a statistically significant improvement in the rate of clinical remission cf. placebo. The placebo rate of remission was 7.4% (95% CI: 2.8 to 12.1%) in Study CB-01-02/01 and 4.5% (95% CI: 0.2 to 8.8%) in Study CB-01-02/02; both were somewhat lower than the value of 13% (95% CI of 9 to 18%) reported in the published literature.[13] Following 8 weeks of treatment with budesonide MMX 9 mg, the remission rate was 17.9% (95% CI: 11.1 to 24.7%) in CB-01-02/01 and 17.4% (95% CI: 10.3 to 24.6%) in Study CB-01-02/02; both were higher than the placebo values in the studies and for values in the published literature, suggesting that the proposed product was effective for induction of clinical remission in the targeted patient population.
- Supportive evidence was also observed in some of the other efficacy endpoints (most noticeably symptom resolution, and less so for histological healing) especially in Study CB-01-02/02. Nevertheless no significant change in the secondary efficacy endpoints (clinical improvement and endoscopic improvement) was apparent in either of the pivotal studies following treatment with budesonide MMX 9 mg, casting some doubt on the actual clinical benefits of the proposed product. In both studies, clinical improvement was linked with endoscopic improvement which was part of the UCDAI used for the measurement of clinical improvement. It is therefore possible that the lack of clinical improvement in these studies may have, at least in part, reflected disagreements and/or variations in endoscopic evaluation especially of proximal colonic lesions, leading to underestimations of changes in the patients (especially those with extensive pancolonic lesions).
- With regards to the non-pivotal studies, there were some significant shortcomings in the design and conduct of these studies. In Study CRO-03-53, patients with only left sided UC were recruited. In Study CB-01-02/05, histological proof of UC was not required for patients entering the study which may at least in part attribute to its substantially higher remission rates than in other studies. The current regulatory guideline requires that 'only patients having confirmed ulcerative colitis should be included in trials'. Caution should therefore be exercised when interpreting the potential clinical relevance of the preliminary efficacy results in the non pivotal studies.

Regarding overall conclusion on safety, the clinical evaluator stated that:

- As an established glucocorticoid, the pharmacological and toxicological profile of budesonide has previously been well characterised and documented.
- With regard to the clinical safety profile of the proposed budesonide MMX 9 mg tablet, relevant data from the pivotal Phase III and non-pivotal Phase II studies showed that the product was safe and generally well tolerated by patients with mild to moderate

[13] Su C, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology*. 2007;132 :516-626.

active UC. The incidences and severity of AEs, treatment related AEs and SAEs were generally similar across all treatment groups in these studies. No deaths have been reported and the reported SAEs were consistent with the events that would be expected, in the targeted patient population with a relapsing and remitting disease. The overall safety profile of the product was generally comparable with that of Entocort which was used as an active comparator in Study CB-01-02/02.

- No unequivocal evidence of glucocorticoid effect was apparent clinically in the submitted studies evaluated. No data on long term use of budesonide was provided. Data was limited to 8 weeks of budesonide treatment.

Following the first round assessment, the clinical evaluator stated that the clinical aspects of the draft Product Information are not entirely satisfactory and suggested revision. Discussion of this is beyond the scope of the AusPAR.

Benefit – risk assessment as per the clinical evaluation - first round

Benefits

The proposed budesonide MMX 9 mg tablet (Cortiment) represents a new formulation of orally administered and topically acting budesonide for the induction of remission in mild to moderate active UC. Given that no oral budesonide formulation is currently available for the treatment of UC and the currently registered Budenofalk enema is suitable only for patients with left sided disease, the proposed Cortiment tablet offers the potential benefit as an alternative option for the proposed indication, especially in patients with proximal involvement of the disease (for example, pancolitis).

The intended once daily dosing regimen for the product also offers a convenient method of treatment and hence potentially assists in better compliance.

Risks

The overall safety profile of the proposed Cortiment tablet following the intended clinical use of 8 weeks has been found to be generally comparable with that of Entocort, another controlled release oral budesonide formulation currently registered on the ARTG for the treatment of Crohn's disease.

Evidence for suppression of the HPA axis was observed, although no unequivocal evidence for glucocorticoid effects was apparent clinically in the submitted studies. The absence of unequivocal evidence for clinically noticeable glucocorticoid effects is not unexpected given the relatively short duration of the clinical studies. The safety profile of the product (Cortiment) following a longer period of clinical use has not been investigated in the submitted clinical studies. Thus, the actual clinical safety of the product beyond the intended 8 week regimen remains largely unknown.

Assessment of benefit-risk balance as per the clinical evaluation (first round)

The benefit-risk balance of the proposed Cortiment tablet, given its intended clinical usage, is considered favourable, as it offers a convenient alternative for the proposed clinical indication with an overall safety profile similar to that of other oral budesonide.

Recommendation regarding authorisation as per the clinical evaluation (first round)

There is no clinical objection to registration of the proposed Cortiment tablet for use of up to 8 weeks for induction of remission in patients with mild to moderate active UC.

Second round evaluation of clinical data submitted in response to clinical questions

The sponsor provided a summary of the maintenance (that is long term of up to 12 weeks) Study CB-01-02/04 as requested by the clinical evaluator. Efficacy analyses revealed no statistically significant differences in the percentages of patients in clinical remission

between budesonide MMX 6 mg and placebo. No long term safety data on the proposed 9 mg daily dose of budesonide MMX was provided.

Risk management plan

An RMP was not required for this submission.

Delegate's discussion

Summary of issues

There were 3 studies with PK data in healthy volunteers (CRO-01-28, CRO-PK-03-105 and CRO-PK-06-178) by Brunner[5].[14] The clinical evaluator stated that the standard PK parameters and absolute bioavailability were not measured at such in these studies but focus rather primarily on GIT transit, release, absorption, bioavailability and influence of food and multiple administrations. The clinical evaluator further stated that no PK study was conducted in the targeted patient population and given the common clinical presentations (especially diarrhoea) in UC patients; it is likely that the GIT transit, absorption and bioavailability of the product in the targeted patient population can be significantly different to those in healthy volunteers. Nevertheless, the available PK data submitted in this application provided sufficient evidence for the targeted and controlled delivery of budesonide to the lower GIT, and supported the proposed once daily dosing regimen as per the clinical evaluation.

The quality evaluator stated that while approval for registration of the proposed product can be recommended from a pharmaceutical chemistry perspective, approval cannot be recommended from a biopharmaceutics perspective. In particular, it is stated that there is a lack of unequivocal conclusion, in terms of the rate and extent of absorption, between the proposed test product Cortiment (1 x 9 mg prolonged release tablet) and the reference product Entocort (3 x 3 mg capsule) in Study CRO-PK-06-178. '*However, whether this lack of unequivocal conclusion has a significant effect on the efficacy and safety profile of the proposed product will be a decision of the Delegate.'*

There were two pivotal efficacy Studies CB-01-01/01 and CB-01-02/02.

Study CB-01-01/01was a multi-centre, randomised, double blind, double dummy, parallel group comparative study in patients with mild or moderate active UC. The study compared the efficacy and safety of budesonide MMX 6 mg and 9 mg tablets with placebo and, also compared Asacol 6 x 400 mg over encapsulated tablets with placebo in four treatment groups over an 8 week treatment period.

Study CB-01-02/02 was a multi-centre, randomised, double blind, double dummy, parallel group comparative design in patients with mild or moderate active UC. The study compared the budesonide MMX 6 mg and 9 mg tablets to placebo and also compared Entocort 3 x 3 mg capsules (9 mg) to placebo over an 8 week treatment period and two other efficacy studies (CRO-03-53- a multi-centre, randomised, 2 period, placebo controlled study, with 4 weeks of blinded treatment (Period 1) followed by 4 weeks of open label extension (Period 2). The main objective of the study was to assess whether the budesonide MMX 9 mg tablet was able to induce a clinical improvement in patients with mild to moderate active left-sided UC.

[14] Brunner M et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol*. 2006;61:31-38.

An additional Study CB-01-02/05 was a multi-centre, randomised, double blind, placebo controlled study. The objective of the study was to evaluate the dose response of budesonide MMX 3 mg and 9 mg oral tablets compared to placebo in patients with mild or moderate active UC, when administered for 8 weeks).

Having commented on the appropriateness of using Entocort as an active efficacy comparator in Study CB-01-02/02, the clinical evaluator stated that the efficacy data from the pivotal studies indicated that the proposed product was effective for induction of clinical remission in the targeted patient population.

With regard to the clinical safety profile of the proposed budesonide MMX 9 mg tablet, the clinical evaluator stated that relevant data from the pivotal Phase III and non pivotal Phase II studies showed that the product was safe and generally well tolerated by patients with mild to moderate active UC and that, no data on long term use of budesonide (that is > 8 weeks) was provided.

Conclusions

The Delegate concurs with the clinical evaluator, that there is sufficient efficacy and safety data to support the registration of budesonide (Cortiment) 9 mg tablet, for the proposed indication of remission in adult patients with mild to moderate active ulcerative colitis for up to 8 weeks. The non-clinical evaluator also aligns with such support. The quality evaluator also supports the registration but has some biopharmaceutical issue concerns. That is, lack of bioequivalence between two different preparations of budesonide (Cortiment and Entocort) in terms of C_{max} and T_{max}. Both C_{max} and T_{max} values for Cortiment (test product) are lower than those for Entocort (reference product). The Delegate believes that those two parameters are not too relevant, considering the local action mechanism of budesonide in the GIT (Cortiment for active UC and Entocort for Crohn's disease (CD)). That is, efficacy of budesonide in UC and CD is not dependent on its systemic pharmacokinetics per se. There are no safety issues of concern either systemically or locally from the evaluated data.

The recommended changes to the PI by both the clinical and non-clinical evaluators are considered acceptable and need to be implemented by the sponsor before finalisation of the application.

The word 'topical' should be replaced with 'local' when describing the action of budesonide. The rationale is that budesonide is taken either orally or rectally to evoke its local action in UC and CD.

The view of the Delegate is that systemic pharmacokinetics of budesonide is not too relevant in this application.

Proposed action

The Delegate had no reason to say, at this time, that the application to register new dosage form of budesonide (Cortiment) for the proposed indication should not be approved for registration subject to resolving issues, arising from the Advisory Committee for Prescription Medicines (ACPM) deliberations and finalisation of matters pertaining to the PI to the satisfaction of the TGA.

Request for ACPM advice

The committee is requested to provide advice on the following specific issue:

1. The view of the Delegate that systemic pharmacokinetics of budesonide is not too relevant in this application.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

The sponsor welcomes the TGA Delegate's pre ACPM preliminary assessment in which the Delegate states '*I have no reason to say, at this time, that the application to register new dosage form of budesonide (Cortiment) for the proposed indication should not be approved for registration*'.

The Delegate has, however, noted one outstanding concern, from the quality evaluation, on the outcomes of the comparative bioavailability Study CRO-PK-06- 178. The clinical relevance of this concern has been referred to the Delegate, who has conveyed the view that the '*systemic pharmacokinetics of budesonide is not too relevant in this application*', but has sought the advice of the ACPM on this position. The sponsor will comment on this concern in the following section of this response.

Biopharmaceutics

As part of the quality evaluation of the Cortiment application, the evaluator raised some technical questions concerning Study CRO-PK-06-178. This study compared the rate and extent of systemic budesonide absorption from Cortiment 9 mg tablets (1 x 9 mg) and three Entocort 3 mg capsules (3 x 3 mg).

Entocort capsules, registered for use in Crohn's disease, are designed to delay commencement of drug release until the dosage form reaches the ileal region, but then to release most of its drug load when transiting through the ileum and ascending colon, areas of the GIT most affected by Crohn's disease. Unlike Crohn's disease, UC affects only the colorectal regions of the GIT. Hence, Cortiment has been developed to preferentially deliver budesonide homogenously along the whole colon.

It is important to put Study CRO-PK-06-178 into perspective. Its objective was not to establish bioequivalence between Cortiment and Entocort, as Cortiment is strictly not a generic of Entocort, given that both products have been designed to release budesonide differently. Indeed, the primary purpose of the trial was to confirm, by way of measuring differences in serum concentration profiles, that budesonide release within the GIT occurs later and in a more prolonged manner with Cortiment than with Entocort, in line with the difference in formulation design between the two products. As orally administered budesonide is thought to act topically on inflamed gastrointestinal mucosa, any differences in the systemic pharmacokinetic characteristics of the two products, as might be borne out in Study CRO-PK-06-178, are not thought to have any direct bearing on the efficacy and safety of these products. Hence the sponsor concurs with the Delegate's view that the '*systemic pharmacokinetics of budesonide is not too relevant in this application*'.

Notwithstanding the sponsor's and the Delegate's position on the questionable clinical relevance of the outcomes of Study CRO-PK-06-178, it is unclear why the quality evaluator remains concerned about the biopharmaceutics results of this study. During two rounds of evaluations, questions on the study were raised, and the sponsor provided answers to these. The matter from the sponsor's perspective is as follows.

In the second round evaluation on quality and biopharmaceutics data, the evaluator had accepted that the Study CRO-PK-06-178 did show that, while the extent of systemic budesonide absorption was similar for Cortiment and Entocort, the determined T_{max} occurred later and C_{max} was lower for Cortiment, consistent with later and more prolonged

release of the budesonide from the dose form. However, the evaluator did not consider this conclusion unequivocal because the information available at that time on the reference product were not fully compliant with requirements of current EU guidelines. The sponsor was therefore asked to justify the absence of this information for the reference product.

In the response, the sponsor explained that, at the time Study CRO-PK-06-178 was conducted (2007), it was not an EU requirement to provide this kind of information for an unmodified reference product. A sensitivity analysis was also performed and submitted showing results in broad agreement with the results of the original calculations. Hence, the sponsor considers that its response to the second round evaluation satisfactorily justified the absence of the requested information and that the conclusions of Study CRO-PK-06-178 are valid.

Conclusion

Cortiment 9 mg tablets are approved in 25 countries and now commercially available in six of these (the United Kingdom (UK), Finland, Germany, Ireland, Austria and the Netherlands). It is also registered and available in the USA under the trade name Uceris 9 mg tablets. The product represents the first orally administered, locally acting corticosteroid formulation that specifically targets drug delivery to the entire colon, the region of the GI tract affected by UC. As acknowledged by the clinical evaluator, the results of the pivotal clinical trials submitted with this application have confirmed that Cortiment is effective and safe in the treatment of mild to moderate active UC. Cortiment would therefore be a novel and valuable addition to the therapeutic options available to Australian clinicians.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Cortiment micronized prolonged-release tablet containing 9 mg of budesonide to have an overall positive benefit–risk profile for the amended indication;

> *Cortiment is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient.*

In making this recommendation the ACPM;

- Noted the PK data presented in healthy individuals were just barely adequate to support the application, given no data were provided in the target population.
- Noted the clinical data did support modest efficacy, however the effect did take 8 weeks.
- Noted the safety profile from the pivotal trials showed that the incidence and rates of AEs of the proposed budesonide MMX 9 mg tablet was generally well tolerated by patients with mild to moderate active UC.
- Noted, however, no data on long term use of budesonide (that is, greater than 8 weeks) were provided.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. The view of the Delegate that systemic pharmacokinetics (PK) of budesonide is not too relevant in this application.

The ACPM agreed overall with the Delegate's view that the PK data provided were just sufficient to reassure but was disappointed that no PK data in Ulcerative Colitis patients were presented, particularly when transit times in the healthy subjects showed such marked variability. It was likely that the GIT transit, absorption and bioavailability of the product in the targeted patient population would be significantly different to those in healthy volunteers. Nevertheless, the PK data submitted in this application provided sufficient evidence for the targeted and controlled delivery of budesonide to the lower GIT, and supported the proposed once-daily dosing regimen.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Post ACPM negotiations

The ACPM recommended the amended indication for the use of Cortiment.

> *Cortiment is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient.*

The sponsor raised concerns that patients who were intolerant to 5-ASA treatment would be precluded under the indication recommended by the ACPM.

The sponsor in correspondence with the Delegate requested an amendment to the indication recommended by the ACPM to:

> *Cortiment is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient or not tolerated.*

The Delegate agreed to the sponsor's proposed amendment to the indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cortiment budesonide 9 mg prolonged release tablet for oral administration blister pack, indicated for:

> *Cortiment is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient or not tolerated.*

Specific conditions of registration applying to these goods

Periodic Safety Update Reports (PSURs) are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's *Guideline on good pharmacovigilance practices (GVP) Module Vll-Periodic Safety Update Report* (Rev I), Part Vll. B. *Structures and processes*. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The Product Information approved for Cortiment at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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