



Australian Government

Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report

Prescription Medicines Authorisation Branch

COR report-based process

Active substance: Omeprazole

Product name: PediPPI

Sponsor: Boucher and Muir

Submission number: PM-2022-02519-1-1

eSubmission number: e006329

First round evaluator:

Date of first round report: 19.10.22

TRIM reference:

Second round evaluator:

Date of second round report:

TRIM reference:

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, 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>>.

Contents

List of abbreviations	5
1. Annotated COR assessment reports	6
2. Australian COR submission details	6
2.1. Differences between the Australian and overseas application	6
2.2. Proposed changes to the product documentation	7
3. Background	7
3.2. Regulatory history	8
3.3. Guidance	11
3.4. Evaluator's commentary on the background information	12
4. Contents of the clinical dossier	12
4.2. Evaluator's commentary on the clinical dossier	13
5. Pharmacokinetics	13
5.2. Evaluator's overall conclusions on pharmacokinetics	15
6. Pharmacodynamics	16
6.2. Evaluator's overall conclusions on pharmacodynamics	17
7. Dosage selection for the pivotal studies	17
7.1. Evaluator's conclusions on dose finding for the pivotal studies	17
8. Clinical efficacy	17
8.1. Evaluator's conclusions on clinical efficacy	18
9. Clinical safety	18
9.2. Adverse events not included in COR assessment	19
9.3. Evaluation of issues with possible regulatory impact	19
9.4. Post marketing experience not assessed by COR report	20
9.5. Evaluator's overall conclusions on clinical safety	20
10. First round benefit-risk assessment	21
10.1. First round assessment of benefits	21
10.2. First round assessment of risks	21
10.3. First round assessment of benefit-risk balance	21
11. First round recommendation regarding authorisation	22
12. First round comments on product documentation	22
12.1. First round comments on draft PI (clinical aspects)	22
12.2. First round comments on draft CMI (clinical aspects)	28
12.3. First round comments on draft RMP (Summary of Safety Concerns)	28

13.	Clinical questions	28
13.1.	PI and CMI	28
14.	First round evaluation errata	29
15.	Second round evaluation	29
16.	Second round benefit-risk assessment	29
17.	Second round recommendation regarding authorisation	29
18.	Second round comments on product documentation	29
19.	References	29
20.	Supporting information, tables and figures	29
21.	Attachment: additional evaluation material	29

List of abbreviations

Abbreviation	Meaning
AUC	Area under the plasma concentration-time curve
C _{max}	Maximum concentration
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
DS	Data Sheet
EMA	European Medicines Agency
EU	European Union
SmPC	Summary of product characteristics
GCP	Good Clinical Practice
GORD	Gastro-oesophageal reflux disease
PD	Pharmacodynamic
PI	Product information
PK	Pharmacokinetic
PPI	Proton pump inhibitor
RMS	Referenced member State
t _{lag}	Time until first non zero concentration
t _{max}	Time of maximum observed concentration

1. Annotated COR assessment reports

There were no annotations to the COR assessment report ([e006329 \(0000-\) - 1.11.4 Foreign evaluation reports - eval-reports-dcp-assess-Final ar](#)).

2. Australian COR submission details

The Sponsor has submitted a Category 1 Type F application to register PEDIPPI omeprazole 2mg/ml and 4mg/ml powder for suspension bottle via the comparable overseas regulator (COR) report-based process (COR-B pathway).

The application is to register the new dosage form and to extend the indication to include children from 1 month of age.

The COR is the European Medical Authority (EMA) via the decentralised procedure with Netherlands as the referenced member state and France, Ireland, United Kingdom and Portugal as contributing concerned members states in the process. The Referenced member State (RMS) approval date was 25 November 2019.

PEDIPPI is an orally administered suspension of omeprazole. Omeprazole is a proton pump inhibitor (PPI) which decreases gastric acid production through inhibition of the H+K+ATPase acid pump.

Omeprazole is available in Australia in a film coated tablet form containing enteric coated omeprazole magnesium pellets in 10 mg and 20 mg strengths and as powder for injection. The reference product Losec (ARTG 63414, 63416) was first registered in 1998.

The COR application checklist was provided in Module 1.2.1 ([e006329 \(0000-\) - 1.7.1 Details of compliance with pre-submission meeting outcomes](#)).

The dossier includes additional manufacturing sites not included in the COR evaluation with validation data for the additional sites provided. As per the checklist the application was eligible for COR-B only based on this aspect. The Final COR was 2 September 2019, there was no new data provided.

2.1. Differences between the Australian and overseas application

Same as assessed/approved by COR?	
Submission type	Type F, new dosage form and extension of indication
Drug class and therapeutic indication	Yes ☒ No ☐ include further information
Dosage forms and strengths	Yes ☒ No ☐ include further information:
Dosage and administration	Yes ☒ No ☐ include further information:

2.2. Proposed changes to the product documentation

The Sponsor has submitted new Product Information (PI) for this indication and dosage form (PediPPI: Omeprazole Powder for oral suspension), see Section 12.

It is based on the Australian Losec tablet PI (enteric coated omeprazole pellets as tablets; 9 March 2021) and includes additional information relevant to the suspension dosage form and extended paediatric indication.

The Sponsor proposes to align the New Zealand and Australia PI, and additions to the PI are also proposed in line with the current NZ Data Sheet (DS) of Losec (gelatine capsules containing enteric coated pellets and enteric coated tablets). The Sponsor proposes to register a common product for the Australian and New Zealand markets, with common product labelling and pack insert.

The therapeutic indications are identical to the approved EU SmPC. The EU SmPC does not include treatment of Zollinger-Ellison Syndrome, which is an approved indication for Losec tablets in Australia.

In adults the dosage instructions are in line with the Australian PI for Losec, with this exception. The proposed paediatric dosage instructions are identical to the Eu SmPC.

3. Background

Section	Page reference in COR report	Acceptable?
Information on the condition being treated	4 – 5	Yes ☒ No ☐
Current treatment options	4 - 5	Yes ☒ No ☐ See additional information below.
Clinical rationale	5	Yes ☒ No ☐ See additional information below.
Formulation: • Formulation development • Excipients	10 – 11, 13 - 14 11	Yes ☒ No ☒ See additional information below

3.1.1. Condition and current treatment options

PediPPI is a new liquid formulation of omeprazole that enables administration to the paediatric population. The main clinical indication is infant gastro-oesophageal reflux disease (GORD) and symptomatic heart burn and acid regurgitation in children over 1 month of age. It is also proposed for treatment of duodenal ulcer caused by *Helicobacter pylori* (*H. pylori*) in combination with antibiotics (in children > 4 years). Other clinical uses include reflux in children with other conditions such as cerebral palsy, congenital oesophageal disorders and cystic fibrosis.

The currently available PPI dosage forms for children (> 1 year old) in Australia included granules in a sachet that are made into a suspension prior to dosing (esomeprazole) or as tablets dispersed in water (omeprazole). Pantoprazole and lansoprazole have granule and dispersible tablet forms but are not registered for use in children below 5 years.

3.1.2. Clinical rationale

In Australia there are no PPIs registered as a liquid suspension and no PPIs registered for use in infants under 1 year.

Omeprazole oral suspension enables accurate dosing in children < 10 kg and from 1 month of age due to the dosage form. Safety and efficacy in infants was addressed in the COR evaluation.

3.1.1. Formulation

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3.2. Regulatory history

3.2.1. Australian regulatory history

Omeprazole as Losec tablets was first approved 14 December 1998.

Omeprazole as an oral suspension has not previously been registered.

Losec tablets are currently indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis.

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective. Zollinger-Ellison Syndrome The treatment of Zollinger-Ellison Syndrome.

Advice for use in children is specified in the dose and method of administration (4.2):

Use in children

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

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

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

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

3.2.2. Orphan drug designation

Not applicable.

3.2.3. Related submissions

There are no related submissions.

3.2.4. Overseas regulatory history

The marketing authorisation status for Omeprazole 2mg/mL and 4mg/mL powder for suspension was provided in Module 1.11.1:

Country/ region	Submission date	Status	Indications (approved or requested)	Other relevant information
European Union decentralised procedure (number: NL/H/4504/001- 002/DC)	01 Aug 2018	Approved. EoP: 02 Sep 2019 RMS approval date: Netherlands: 25 November 2019 CMS national approval dates: France: 01 Jun 2021 Ireland: 15 Nov 2019 United Kingdom: 01 Oct 2019 Portugal: 07 Jan 2020	<p>Adults</p> <ul style="list-style-type: none"> • Treatment of duodenal ulcers • Prevention of relapse of duodenal ulcers • Treatment of gastric ulcers • Prevention of relapse of gastric ulcers • In combination with appropriate antibiotics, <i>Helicobacter pylori</i> (<i>H. pylori</i>) eradication in peptic ulcer disease • Treatment of NSAID-associated gastric and duodenal ulcers • Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk • Treatment of reflux esophagitis • Long-term management of patients with healed reflux esophagitis • Treatment of symptomatic gastro-esophageal reflux disease <p>Paediatric use</p> <p><u>Children over 1 month of age</u></p> <ul style="list-style-type: none"> • Treatment of reflux esophagitis • Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease <p><u>Children over 4 years of age and adolescents</u> In combination with antibiotics in treatment of duodenal ulcer caused by <i>H. pylori</i></p>	<p>Please note that IP/MA holder is Xeolas Pharmaceuticals Limited.</p> <p>Advanz Pharma (Australia) has licensed the rights to the product for Australia and New Zealand from Xeolas Pharmaceuticals Limited.</p>

New Zealand	12 Mar 2021	Approved. Consent given: 12 May 2022	<p>PediPPI is indicated for the treatment of:</p> <ul style="list-style-type: none"> • reflux oesophagitis • duodenal ulcer • gastric ulcer • NSAID-associated gastric and duodenal ulcers or erosions • symptoms of acid related dyspepsia • Zollinger-Ellison syndrome. <p>In the treatment of peptic ulceration, the eradication of <i>H. pylori</i>, as the causative organism, must be a high priority. Accordingly, PediPPI should be used as part of combination therapy for the eradication of <i>H. pylori</i>.</p> <p>Maintenance PediPPI is indicated for maintenance treatment of:</p> <ul style="list-style-type: none"> • reflux oesophagitis • duodenal ulcer • gastric ulcer • Zollinger-Ellison syndrome. <p>Children over 1 month of age</p> <ul style="list-style-type: none"> • Treatment of reflux oesophagitis • Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease. 	<p>Please note that MA holder is Boucher & Muir (New Zealand) Limited which is a wholly owned subsidiary of Boucher & Muir Pty Ltd t/a Advanz Pharma (Australia).</p> <p>Advanz Pharma (Australia) has licensed the rights to the product for Australia and New Zealand from Xeolas Pharmaceuticals Limited (EU IP/MA holder).</p>
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The Sponsor states no applications have been deferred or withdrawn.

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3.3. Guidance

Pre-submission advice was sought by the Sponsor in relation to the COR pathway, trade name, product information, use of an overseas reference product and RMP (see Module 1.7.1 [e006329 \(0000-\) - 1.7.1 Details of compliance with pre-submission meeting outcomes](#)).

The Sponsor sought guidance on the PI for the oral suspension. A blend of the Australian PI for Losec and the EU approved Summary of product characteristics (SmPC) was proposed. Challenges in bridging the two were raised and included the wording for indications in the paediatric population, particularly children < 1 year and use in Zollinger-Ellison Syndrome.

In order to resolve this the Sponsor has submitted proposed therapeutic indications that specify age groups for treatment in adults and children which align with the EU SmPC. The proposed

therapeutic indications group children from ≥ 1 month of age with narrower proposed therapeutic indications than the current Losec PI (indicated for children > 1 year). Zollinger-Ellison was removed as an indication.

Confirmation of the suitability of the COR evaluated paediatric data was also obtained, which included a Pharmacodynamic (PD)/efficacy study in infants (Study DA 04/07) plus a Pharmacokinetic (PK) study which bridges efficacy/safety data. No Risk Management Plan was required for this submission.

The proposed additional drug substance manufacturing site will be approved by a post-approval application.

The following TGA guidelines are considered relevant to this submission:

- Australian Regulatory Guidelines for Prescription Medicines <https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm>
- Form for providing product information <https://www.tga.gov.au/form-providing-product-information>

The following international guidelines are considered relevant to this submission:

- EMA guideline on clinical investigation of medicinal products in the paediatric population [E11\(R1\) Step 5 Clinical investigation of medicinal products in the paediatric population \(europa.eu\)](https://www.ema.europa.eu/en/clinical-investigation-guidelines-paediatric)

3.4. Evaluator's commentary on the background information

The background information is satisfactory.

4. Contents of the clinical dossier

Section	Page reference in COR report	Acceptable?
Scope of the clinical dossier	13 – 25	Yes ☒ No ☐
Paediatric data	16 – 17, 21 - 23	Yes ☒ No ☐
Good clinical practice	9	Yes ☒ No ☐

4.1.1. Scope of the clinical dossier

Table 1 provides an overview of the clinical studies supporting registration evaluated in the COR evaluation report:

Table 1 Tabular listing of all clinical studies

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4.2. Evaluator's commentary on the clinical dossier

The clinical dossier is satisfactory. This evaluation is based on the COR assessment reports provided in Module 1.11.4. Module 2 summaries were referred to.

5. Pharmacokinetics

Section	Page reference in COR report	Acceptable?
Studies providing pharmacokinetic information	14 - 15, 17 -18	Yes ☒ No ☐
Summary of pharmacokinetics	14 - 15, 18 -19	Yes ☒ No ☐
Physicochemical characteristics of the active substance	N/A	Yes ☐ No ☐

Pharmacokinetics in healthy subjects: <ul style="list-style-type: none"> • Absorption • Bioavailability • Distribution • Metabolism • Excretion 	17	Yes ☒ No ☐
Intra and inter individual variability of pharmacokinetics	N/A	Yes ☐ No ☐
Pharmacokinetics in the target population	17	Yes ☒ No ☐
Pharmacokinetics in special populations <ul style="list-style-type: none"> • Pharmacokinetics in subjects with impaired hepatic function • Pharmacokinetics in subjects with impaired renal function • Pharmacokinetics according to age • Pharmacokinetics related to genetic factors • Pharmacokinetics in other special population / with other population characteristic 	N/A	Yes ☐ No ☐
Population pharmacokinetics	17	Yes ☒ No ☐
Pharmacokinetic interactions	N/A	Yes ☐ No ☐
Clinical implications of in vitro findings	N/A	Yes ☐ No ☐

5.1.1. Bioavailability/bioequivalence

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5.1.2. Population PK model

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5.2. Evaluator's overall conclusions on pharmacokinetics

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6. Pharmacodynamics

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Studies providing pharmacodynamic information	15 - 19	Yes ☒ No ☐ See additional information below.
Summary of pharmacodynamics <ul style="list-style-type: none"> • Mechanism of action • Pharmacodynamic effects (primary and secondary) • Time course of pharmacodynamic effects • Relationship between drug concentration and pharmacodynamic effects • Genetic, gender and age related differences in pharmacodynamic response • Pharmacodynamic interactions 	16 - 19	Yes ☒ No ☐

6.1.1. Study BA 04/07: supportive pharmacodynamic/ safety/efficacy paediatric study

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6.2. Evaluator's overall conclusions on pharmacodynamics

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7. Dosage selection for the pivotal studies

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Pharmacokinetics and pharmacodynamics: dose finding studies	17	Yes ☐ No ☐
Phase II dose finding studies	N/A	Yes ☐ No ☐
Phase III pivotal studies investigating more than one dose regimen	N/A	Yes ☐ No ☐

7.1. Evaluator's conclusions on dose finding for the pivotal studies

See Section 5.2 and 6.2.

8. Clinical efficacy

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Studies providing evaluable efficacy data	16	Yes ☒ No ☐
Pivotal or main efficacy studies	16	Yes ☒ No ☐
Phase III pivotal studies investigating more than one dose regimen	N/A	Yes ☐ No ☐

Other efficacy studies	N/A	Yes ☐ No ☐
Analyses performed across trials: pooled and meta analyses	N/A	Yes ☐ No ☐

8.1. Evaluator's conclusions on clinical efficacy

See Section 6.2.

9. Clinical safety

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
<p>Studies providing evaluable safety data:</p> <ul style="list-style-type: none"> Pivotal studies that assessed safety as the sole primary outcome Pivotal and/or main efficacy studies Other studies: <ul style="list-style-type: none"> Studies with evaluable safety data: dose finding and pharmacology Studies evaluable for safety only 	<p>N/A</p> <p>21 -23</p> <p>20, 21</p>	<p>Yes ☒ No ☐</p>
Studies that assessed safety as the sole primary outcome	N/A	Yes ☐ No ☐
Patient exposure	19	Yes ☒ No ☐
<p>Adverse events:</p> <ul style="list-style-type: none"> All adverse events (irrespective of relationship to study treatment) Treatment related adverse events (adverse drug reactions) Deaths and other serious adverse events 	19, 22	Yes ☒ No ☐

- | | | |
|--|--|--|
| <ul style="list-style-type: none"> Discontinuations due to adverse events | | |
|--|--|--|

9.1.1. Oral suspension safety data

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9.1.2. Paediatric safety data evaluation

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9.2. Adverse events not included in COR assessment

N/A

9.3. Evaluation of issues with possible regulatory impact

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Liver function and liver toxicity	N/A	Yes ☐ No ☐
Renal function and renal toxicity	N/A	Yes ☐ No ☐
Other clinical chemistry	N/A	Yes ☐ No ☐
Haematology and haematological toxicity	N/A	Yes ☐ No ☐
Other laboratory tests	N/A	Yes ☐ No ☐

¹ Summary on page 446 -449 of [e006329 \(0000-\) - 5.4 Literature References - Common](#)

² Article p 781 of [e006329 \(0000-\) - 5.4 Literature References - Common](#); Characteristics of Children Receiving Proton Pump Inhibitors Continuously for Up to 11 Years Duration Hassal E, Kerr W., Hashem B Journal of Pediatrics V150, 2007 p 262-267

Electrocardiograph findings and cardiovascular safety	N/A	Yes ☐ No ☐
Vital signs and clinical examination findings	N/A	Yes ☐ No ☐
Immunogenicity and immunological events	N/A	Yes ☐ No ☐
Serious skin reactions	N/A	Yes ☐ No ☐
Other safety parameters	N/A	Yes ☐ No ☐
Other safety issues	N/A	Yes ☐ No ☐
Post marketing experience	N/A	Yes ☐ No ☐

9.4. Post marketing experience not assessed by COR report

N/A

9.5. Evaluator's overall conclusions on clinical safety

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10. First round benefit-risk assessment

10.1. First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Oral suspension omeprazole provides an alternative route of administration for the treatment of reflux in paediatric and adult patients.	Currently available omeprazole requires suspension of granules prior to use and administration by caregivers as a liquid.
The oral suspension formulation enables more accurate dosing, particularly in patients under 10 kg requiring doses below 10 mg.	
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10.2. First round assessment of risks

Risks	Strengths and Uncertainties
s47	s47

10.3. First round assessment of benefit-risk balance

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11. First round recommendation regarding authorisation

At this stage there is no clinical objection to registration of PediPPI omeprazole oral suspension 2mg/mL and 4mg/mL subject to satisfactory response to the Clinical questions.

12. First round comments on product documentation

The following comments relate to the proposed PediPPI PI provided in Module 1.3, Sequence 0000 ([e006329 \(0000-\) - 1.3.1.2 Product information - annotated - 0000](#)).

As per the comments in Section 2.2, the PI for PediPPI Omeprazole Powder for oral suspension, is new. It is based on the Australian Losec PI ([Local Product Information - Australia \(tga.gov.au\)](#)) using the EU SmPC ([e006329 \(0000-\) - 1.11.2 Foreign product information](#)) for indications and instructions relevant to the oral suspension formulation and paediatric dosing.

There are also additions to the PI proposed in line with the current NZ Data Sheet of Losec ([e006329 \(0000-\) - 1.11.2 Foreign product information](#)).

12.1. First round comments on draft PI (clinical aspects)

Proposed
<p>4.1 Therapeutic indications</p> <p><u>Adults</u></p> <ul style="list-style-type: none"> ▪ Treatment of duodenal ulcers ▪ Prevention of relapse of duodenal ulcers ▪ Treatment of gastric ulcers ▪ Prevention of relapse of gastric ulcers ▪ In combination with appropriate antibiotics, <i>Helicobacter pylori</i> (<i>H. pylori</i>) eradication in peptic ulcer disease ▪ Treatment of NSAID-associated gastric and duodenal ulcers ▪ Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk ▪ Treatment of reflux oesophagitis ▪ Long-term management of patients with healed reflux oesophagitis ▪ Treatment of symptomatic gastro-oesophageal reflux disease (GORD) <p><u>Paediatric use</u></p> <p><u>Children over 1 month of age</u></p> <ul style="list-style-type: none"> ▪ Treatment of reflux oesophagitis ▪ Symptomatic treatment of heartburn and acid regurgitation in GORD <p><u>Children over 4 years of age and adolescents</u></p> <p>In combination with antibiotics in treatment of duodenal ulcer caused by <i>H. pylori</i></p> <p>P2</p> <p>Section 4.1 aligns with the EU SmPC.</p>

The wording differs from the current Australian Losec PI, but the conditions for which it is indicated to treat and prevent relapse remain the same, with the exception of Zollinger Ellison syndrome.

The Sponsor indicated a large volume of omeprazole oral suspension would be required to achieve treatment doses (60 mg omeprazole daily initially titrated up or down) and the bottle size (2mg/mL: total bottle 180 mg of omeprazole; 4mg/mL: total bottle 360 mg) does not cater for the volumes required. The 4 mg/mL bottle would last 6 doses at 60 mL each dose.

The indications for paediatric use are aligned with the EU SmPC. The current Losec PI does not include separate therapeutic indications for paediatric patients. Guidance use in paediatric patients from 1 year is provided in the Section 4.2 Dose and Method of Administration.

The rationale for not including Zollinger Ellison as an indication is acceptable. Alternative treatment options are available to better cater for the required high dose.

*The wording for the indications of gastric and duodenal ulcers, treatment of *H. pylori*, NSAID associated gastric and duodenal ulcers, reflux oesophagitis and gastro-oesophageal reflux disease is in line with the current Losec PI, is clear, and is accepted.*

The paediatric indications are acceptable for the Australian PI.

Proposed

4.2 Dose and method of administration

PediPPI is recommended to be given in the morning.

Commented [s22]: Added in line with Losec NZ Data Sheet

PediPPI 2 mg/mL oral suspension is suitable for doses of ≤ 15 mg. For doses of 20 mg or greater, PediPPI 4 mg/mL oral suspension is suitable.

Commented [s23]: Added in line with PEDIPPI SmPC, as specific for suspension dosage form

P3

The advice on dosing in the morning is not present in the current Losec PI or EU SmPC but is based on the NZ data sheet. Indication has not been provided as to why this was required in NZ.

Indication as to why a morning dose was a requirement in the NZ DS will need to be provided by the Sponsor (see Clinical questions Section 13.1).

The advice on the available suspension forms and suitability based on target dose, as per the EU SmPC, is accepted.

Zollinger-Ellison Syndrome

Recommended initial dose: omeprazole 60 mg once daily.

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

Use in children

Children over 1 month of age

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in GORD

Age	Weight	Dose*
1 month to 1 year of age	--	1 mg/kg once daily. Doses above 1.5 mg/kg/day have not been studied.
≥ 1 year of age	10 - 20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed.

* Individual dose measurements ≤ 2 mL of the 2 mg/mL presentation are not indicated.

The 2 mg/mL and 4 mg/mL strengths are equivalent with respect to buffering capacity (same amount of buffer on a mL basis).

For doses of ≤ 15 mg, the 2 mg/mL strength is recommended. The 2 mg/mL strength is indicated for age 1 month to 1 year for administering up to 15 mg, and ≥ 1 year of age for administering 10 mg, to provide sufficient buffering capacity and absorption.

For doses of 20 mg or 40 mg, the 4 mg/mL strength is suitable. The 4 mg/mL strength is indicated for administration of 20 mg or 40 mg so that a maximum of 2 doses are required.

Reflux oesophagitis: The treatment time is 4 - 8 weeks.

Commented s22.1: Dosage information for Zollinger-Ellison syndrome, present in the approved Product Information for Losec Tablets, has been removed as this indication is not included in the approved PEDIPPI SmPC and consequently not proposed for the AU PI for PediPPI.

Please also refer to the DIRECTIONS FOR EVALUATORS TO THE EVIDENCE BASE FOR THIS PI on the cover page for this PI regarding the indication of Zollinger-Ellison Syndrome.

Commented s22.0: This entire sub-section is included in line with the approved PEDIPPI SmPC.

Commented s22.1j: Note for information: The dosage for children over 1 year of age is identical to the approved dosage in Losec Tablets AU PI.

Commented s22.2j: Please note this statement is specific to the 2 mg/mL strength and only included in the approved PEDIPPI SPC for the 2 mg/mL strength. It is not included in the approved PEDIPPI SPC for the 4 mg/mL strength. Since the PI covers information for both strengths, the words "of the 2 mg/mL presentation" have been added to the statement to ensure the information is attributed to the correct strength.

P5

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease: The treatment time is 2 - 4 weeks. If symptom control has not been achieved after 2 - 4 weeks the patient should be investigated further.

Children over 4 years of age and adolescents

- Treatment of duodenal ulcer caused by *H. pylori*

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

Weight	Dose
15 - 30 kg	Combination with two antibiotics: omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together two times daily for one week.
31 - 40 kg	Combination with two antibiotics: omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered two times daily for one week.
> 40 kg	Combination with two antibiotics: omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered two times daily for one week.

Elderly

No dosage adjustment of omeprazole is necessary in the elderly.

Hepatic impairment

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

Renal impairment

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

Commented s22.3j: As noted above, the *Use in children* section is based on the approved PEDIPPI SPC, and proposed to be included in the AU PI as a consequence of including the corresponding paediatric indication as per the approved PEDIPPI SPC.

In addition for this particular sub-section, the sponsor proposes to further amend the present proposed dosage information for Australia by removing the specific names and dosage for the antibiotics mentioned in the SPC, as no such indication and/or dosage is contained in the AU Losec tablets PI dated 09 March 2021, the AU Klocid PI dated 18 September 2019 or the Amoxal PI dated 06 May 2022.

However, it is of note that this dosage information is included in the UK SPC for Losec Capsules 20 mg, MA holder AstraZeneca UK Ltd, dated 19 May 2017 (please refer to Module 1.11.2).

Method of administration

Omeprazole oral suspension should be taken on an empty stomach, at least 30 minutes before a meal.

Precautions to be taken before handling or administering the medicinal product

Omeprazole powder for oral suspension requires reconstitution prior to oral administration. For instructions on reconstitution of the medicinal product before administration, see Section 6.6. Special precautions for disposal.

For instructions for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes (see Section 6.6. Special precautions for disposal).

Commented [522]: All text under this heading is taken from the approved PEDIPPI SmPC as it is specific for suspension dosage form.

P6

The discussion of removal of advice on Zollinger-Ellison Syndrome is discussed above.

The prescribing advice for use in children aligns with the EU SmP. The prescribing advice for treatment of *H. pylori* aligns with the Losec PI.

Method of administration aligns with the Eu SmPC.

The proposed prescribing advice for children is accepted as is the method of administration.

Proposed

4.4 Special warnings and precautions for use

Hypomagnesaemia

Symptomatic hypomagnesaemia has been reported rarely in patients treated with long-term PPI medication. In some severe cases hypocalcaemia was also reported. Severe hypomagnesaemia may result in serious adverse events such as tetany, seizures and potentially also arrhythmias. In some patients, treatment of hypomagnesaemia with magnesium replacement was not sufficient to correct the magnesium imbalance and discontinuation of the PPI was required. In patients later retreated with the same or different PPI, hypomagnesaemia returned within a shorter time period. For patients expected to be on prolonged treatment or who take PPIs with other medicines such as digoxin or medicines that may cause hypomagnesaemia, consideration should be given to monitoring magnesium levels prior to initiation and periodically thereafter.

Use in hepatic impairment

Commented [522]: This section is additional and was added based on NZ DS of Losec, and is also in line with approved SmPC of PEDIPPI. AU PI for Losec tablets also mentions this, but in the AE section.

P8

Inclusion of hypomagnesaemia in this section to align with the NZ DS is acceptable.

Proposed

4.5 Interactions with other medicines and other forms of interactions

Citalopram / Escitalopram

Co-administration of omeprazole (20 mg) with citalopram (20 mg single dose) doubles the AUC of the S-isomer of citalopram, but the R-isomer of citalopram is not affected. A reduction in the dose of citalopram may be necessary based on clinical judgement. For patients taking omeprazole, the citalopram dose should not exceed the maximum dose of 20 mg/day.

Co-administration of omeprazole (30 mg) with escitalopram (20 mg single dose) increased the plasma levels (approximately 50%) and terminal half-life (31%) of escitalopram. A reduction in the dose of escitalopram may be necessary based on clinical judgement.

Effects of other drugs on omeprazole

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

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

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

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

Potential interactions that have been excluded

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

Commented ^{s22} 16]: Proposed to be added in line with NZ DS of Losec.

Commented ^{s22} 7]: Proposed to be added in line with NZ DS of Losec.

P11

Inclusion of the paragraph on citalopram/ escitalopram interaction and addition of 2 medications that do not interact with omeprazole are proposed to align with the NZ DS.

Indication as to why these differences are present in the NZ DS will need to be provided by the Sponsor (see Clinical questions Section 13).

Proposed

4.6 Fertility, Pregnancy and Lactation

Use in pregnancy (Category B3)

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

Commented ^{s22} 8]: In line with approved AU PI for Losec tablets

P12

Use in pregnancy category of B3 is accepted.

Proposed

4.8 Adverse effects (undesirable effects)

Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

Reporting suspected adverse effects

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

Commented [s22 9]: This section is relevant information on adverse effects applicable to the extended paediatric population as per the approved PEDIPPI SmPC and is therefore proposed for inclusion in the PI.

P14

Inclusion of the paragraph on safety in the paediatric population aligns with the EU SmPC and is accepted.

Proposed

5.1 Pharmacodynamic properties

In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90% of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0 – 24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of the dose.

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

Commented [s22 10]: This information is related to the extended paediatric population and is proposed in line with the approved PEDIPPI SmPC.

P17

Inclusion of the paragraph on pharmacodynamic properties in the paediatric population aligns with the EU SmPC and is accepted.

Proposed

5.2 Pharmacokinetic properties

Absorption

Omeprazole is acid labile and is therefore administered in omeprazole oral suspension as a buffered suspension. The buffer protects omeprazole from acid degradation, facilitating absorption.

Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 30 minutes after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3 - 6 hours. In a bioavailability study, the administration with food (milk) reduced the extent of absorption by approximately 20%. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Commented [s22:1]: Absorption section proposed in line with PEDIPPI SmPC as related to the oral suspension dosage form

Distribution

P17

In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

Commented [s22:2]: This information is related to the extended paediatric population and is included in line with the approved PEDIPPI SmPC.

P18

Inclusion of the paragraph on pharmacokinetic properties in the paediatric population aligns with the EU SmPC and is accepted.

12.2. First round comments on draft CMI (clinical aspects)

The Sponsor included a CMI in Module 1.3.2.1 ([e006329 \(0000-\) - 1.3.2.1 Consumer medicines information - clean - 0000](#)). This is a new CMI proposed for Australia and New Zealand.

The CMI was acceptable. Inclusion of citalopram/escitalopram as an interaction was noted and is accepted pending provision of the relevant clinical information (See Section 13).

12.3. First round comments on draft RMP (Summary of Safety Concerns)

No Risk Management Plan was required for this submission.

13. Clinical questions

13.1. PI and CMI

s47

14. First round evaluation errata

N/A

15. Second round evaluation

N/A

16. Second round benefit-risk assessment

N/A

**17. Second round recommendation regarding
authorisation**

N/A

18. Second round comments on product documentation

N/A

19. References

N/A

20. Supporting information, tables and figures

N/A

21. Attachment: additional evaluation material

N/A

Therapeutic Goods Administration

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<https://www.tga.gov.au>



Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report

Prescription Medicines Authorisation Branch

COR report-based process

Active substance: Omeprazole

Product name: Omeprazole ADVZ¹

Sponsor: Boucher and Muir

Submission number: PM-2022-02519-1-1

eSubmission number: e006329

First round evaluator:

Date of first round report: 19.10.22

TRIM reference:

Second round evaluator:

Date of second round report: 30.01.22

TRIM reference:

¹ The proposed name changed from PediPPI to Omeprazole ADVZ during the course of the evaluation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, 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>>.

Contents

List of abbreviations	5
1. Annotated COR assessment reports	6
2. Australian COR submission details	6
2.1. Differences between the Australian and overseas application	6
2.2. Proposed changes to the product documentation	7
3. Background	7
3.2. Regulatory history	8
3.3. Guidance	11
3.4. Evaluator's commentary on the background information	12
4. Contents of the clinical dossier	12
4.2. Evaluator's commentary on the clinical dossier	13
5. Pharmacokinetics	13
5.2. Evaluator's overall conclusions on pharmacokinetics	15
6. Pharmacodynamics	16
6.2. Evaluator's overall conclusions on pharmacodynamics	17
7. Dosage selection for the pivotal studies	17
7.1. Evaluator's conclusions on dose finding for the pivotal studies	17
8. Clinical efficacy	17
8.1. Evaluator's conclusions on clinical efficacy	18
9. Clinical safety	18
9.2. Adverse events not included in COR assessment	19
9.3. Evaluation of issues with possible regulatory impact	19
9.4. Post marketing experience not assessed by COR report	20
9.5. Evaluator's overall conclusions on clinical safety	20
10. First round benefit-risk assessment	21
10.1. First round assessment of benefits	21
10.2. First round assessment of risks	21
10.3. First round assessment of benefit-risk balance	21
11. First round recommendation regarding authorisation	22
12. First round comments on product documentation	22
12.1. First round comments on draft PI (clinical aspects)	22
12.2. First round comments on draft CMI (clinical aspects)	28
12.3. First round comments on draft RMP (Summary of Safety Concerns)	28

13.	Clinical questions	28
13.1.	PI and CMI	28
14.	First round evaluation errata	29
15.	Second round evaluation	29
15.1.	Response to Clinical Questions	29
16.	Second round benefit-risk assessment	29
17.	Second round recommendation regarding authorisation	29
18.	Second round comments on product documentation	30
19.	References	30
20.	Supporting information, tables and figures	30
21.	Attachment: additional evaluation material	30

List of abbreviations

Abbreviation	Meaning
AUC	Area under the plasma concentration-time curve
C _{max}	Maximum concentration
CMI	Consumer Medicine Information
COR	Comparable Overseas Regulator
DS	Data Sheet
EMA	European Medicines Agency
EU	European Union
SmPC	Summary of product characteristics
GCP	Good Clinical Practice
GORD	Gastro-oesophageal reflux disease
PD	Pharmacodynamic
PI	Product information
PK	Pharmacokinetic
PPI	Proton pump inhibitor
RMS	Referenced member State
t _{lag}	Time until first non zero concentration
t _{max}	Time of maximum observed concentration

1. Annotated COR assessment reports

There were no annotations to the COR assessment report ([e006329 \(0000-\) - 1.11.4 Foreign evaluation reports - eval-reports-dcp-assess-Final ar](#)).

2. Australian COR submission details

The Sponsor has submitted a Category 1 Type F application to register PEDIPPI omeprazole 2mg/ml and 4mg/ml powder for suspension bottle via the comparable overseas regulator (COR) report-based process (COR-B pathway).

The application is to register the new dosage form and to extend the indication to include children from 1 month of age.

The COR is the European Medical Authority (EMA) via the decentralised procedure with Netherlands as the referenced member state and France, Ireland, United Kingdom and Portugal as contributing concerned members states in the process. The Referenced member State (RMS) approval date was 25 November 2019.

PEDIPPI is an orally administered suspension of omeprazole. Omeprazole is a proton pump inhibitor (PPI) which decreases gastric acid production through inhibition of the H+K+ATPase acid pump.

Omeprazole is available in Australia in a film coated tablet form containing enteric coated omeprazole magnesium pellets in 10 mg and 20 mg strengths and as powder for injection. The reference product Losec (ARTG 63414, 63416) was first registered in 1998.

The COR application checklist was provided in Module 1.2.1 ([e006329 \(0000-\) - 1.7.1 Details of compliance with pre-submission meeting outcomes](#)).

The dossier includes additional manufacturing sites not included in the COR evaluation with validation data for the additional sites provided. As per the checklist the application was eligible for COR-B only based on this aspect. The Final COR was 2 September 2019, there was no new data provided.

2.1. Differences between the Australian and overseas application

Same as assessed/approved by COR?	
Submission type	Type F, new dosage form and extension of indication
Drug class and therapeutic indication	Yes ☒ No ☐ include further information
Dosage forms and strengths	Yes ☒ No ☐ include further information:
Dosage and administration	Yes ☒ No ☐ include further information:

2.2. Proposed changes to the product documentation

The Sponsor has submitted new Product Information (PI) for this indication and dosage form (PediPPI: Omeprazole Powder for oral suspension), see Section 12.

It is based on the Australian Losec tablet PI (enteric coated omeprazole pellets as tablets; 9 March 2021) and includes additional information relevant to the suspension dosage form and extended paediatric indication.

The Sponsor proposes to align the New Zealand and Australia PI, and additions to the PI are also proposed in line with the current NZ Data Sheet (DS) of Losec (gelatine capsules containing enteric coated pellets and enteric coated tablets). The Sponsor proposes to register a common product for the Australian and New Zealand markets, with common product labelling and pack insert.

The therapeutic indications are identical to the approved EU SmPC. The EU SmPC does not include treatment of Zollinger-Ellison Syndrome, which is an approved indication for Losec tablets in Australia.

In adults the dosage instructions are in line with the Australian PI for Losec, with this exception. The proposed paediatric dosage instructions are identical to the Eu SmPC.

3. Background

Section	Page reference in COR report	Acceptable?
Information on the condition being treated	4 – 5	Yes ☒ No ☐
Current treatment options	4 - 5	Yes ☒ No ☐ See additional information below.
Clinical rationale	5	Yes ☒ No ☐ See additional information below.
Formulation: • Formulation development • Excipients	10 – 11, 13 - 14 11	Yes ☒ No ☒ See additional information below

3.1.1. Condition and current treatment options

PediPPI is a new liquid formulation of omeprazole that enables administration to the paediatric population. The main clinical indication is infant gastro-oesophageal reflux disease (GORD) and symptomatic heart burn and acid regurgitation in children over 1 month of age. It is also proposed for treatment of duodenal ulcer caused by *Helicobacter pylori* (*H. pylori*) in combination with antibiotics (in children > 4 years). Other clinical uses include reflux in children with other conditions such as cerebral palsy, congenital oesophageal disorders and cystic fibrosis.

The currently available PPI dosage forms for children (> 1 year old) in Australia included granules in a sachet that are made into a suspension prior to dosing (esomeprazole) or as tablets dispersed in water (omeprazole). Pantoprazole and lansoprazole have granule and dispersible tablet forms but are not registered for use in children below 5 years.

3.1.2. Clinical rationale

In Australia there are no PPIs registered as a liquid suspension and no PPIs registered for use in infants under 1 year.

Omeprazole oral suspension enables accurate dosing in children < 10 kg and from 1 month of age due to the dosage form. Safety and efficacy in infants were addressed in the COR evaluation.

3.1.1. Formulation

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3.2. Regulatory history

3.2.1. Australian regulatory history

Omeprazole as Losec tablets was first approved 14 December 1998.

Omeprazole as an oral suspension has not previously been registered.

Losec tablets are currently indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis.

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

Advice for use in children is specified in the dose and method of administration (4.2):

Use in children

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

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

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

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

3.2.2. Orphan drug designation

Not applicable.

3.2.3. Related submissions

There are no related submissions.

3.2.4. Overseas regulatory history

The marketing authorisation status for Omeprazole 2mg/mL and 4mg/mL powder for suspension was provided in Module 1.11.1:

Country/ region	Submission date	Status	Indications (approved or requested)	Other relevant information
European Union decentralised procedure (number: NL/H/4504/001- 002/DC)	01 Aug 2018	Approved. EoP: 02 Sep 2019 RMS approval date: Netherlands: 25 November 2019 CMS national approval dates: France: 01 Jun 2021 Ireland: 15 Nov 2019 United Kingdom: 01 Oct 2019 Portugal: 07 Jan 2020	<p>Adults</p> <ul style="list-style-type: none"> • Treatment of duodenal ulcers • Prevention of relapse of duodenal ulcers • Treatment of gastric ulcers • Prevention of relapse of gastric ulcers • In combination with appropriate antibiotics, <i>Helicobacter pylori</i> (<i>H. pylori</i>) eradication in peptic ulcer disease • Treatment of NSAID-associated gastric and duodenal ulcers • Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk • Treatment of reflux esophagitis • Long-term management of patients with healed reflux esophagitis • Treatment of symptomatic gastro-esophageal reflux disease <p>Paediatric use</p> <p><u>Children over 1 month of age</u></p> <ul style="list-style-type: none"> • Treatment of reflux esophagitis • Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease <p><u>Children over 4 years of age and adolescents</u> In combination with antibiotics in treatment of duodenal ulcer caused by <i>H. pylori</i></p>	<p>Please note that IP/MA holder is Xeolas Pharmaceuticals Limited.</p> <p>Advanz Pharma (Australia) has licensed the rights to the product for Australia and New Zealand from Xeolas Pharmaceuticals Limited.</p>

New Zealand	12 Mar 2021	Approved. Consent given: 12 May 2022	<p>PediPPI is indicated for the treatment of:</p> <ul style="list-style-type: none"> • reflux oesophagitis • duodenal ulcer • gastric ulcer • NSAID-associated gastric and duodenal ulcers or erosions • symptoms of acid related dyspepsia • Zollinger-Ellison syndrome. <p>In the treatment of peptic ulceration, the eradication of <i>H. pylori</i>, as the causative organism, must be a high priority. Accordingly, PediPPI should be used as part of combination therapy for the eradication of <i>H. pylori</i>.</p> <p>Maintenance PediPPI is indicated for maintenance treatment of:</p> <ul style="list-style-type: none"> • reflux oesophagitis • duodenal ulcer • gastric ulcer • Zollinger-Ellison syndrome. <p>Children over 1 month of age</p> <ul style="list-style-type: none"> • Treatment of reflux oesophagitis • Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease. 	<p>Please note that MA holder is Boucher & Muir (New Zealand) Limited which is a wholly owned subsidiary of Boucher & Muir Pty Ltd t/a Advanz Pharma (Australia).</p> <p>Advanz Pharma (Australia) has licensed the rights to the product for Australia and New Zealand from Xeolas Pharmaceuticals Limited (EU IP/MA holder).</p>
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The Sponsor states no applications have been deferred or withdrawn.

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3.3. Guidance

Pre-submission advice was sought by the Sponsor in relation to the COR pathway, trade name, product information, use of an overseas reference product and RMP (see Module 1.7.1 [e006329 \(0000-\) - 1.7.1 Details of compliance with pre-submission meeting outcomes](#)).

The Sponsor sought guidance on the PI for the oral suspension. A blend of the Australian PI for Losec and the EU approved Summary of product characteristics (SmPC) was proposed. Challenges in bridging the two were raised and included the wording for indications in the paediatric population, particularly children < 1 year and use in Zollinger-Ellison Syndrome.

In order to resolve this the Sponsor has submitted proposed therapeutic indications that specify age groups for treatment in adults and children which align with the EU SmPC. The proposed

therapeutic indications group children from ≥ 1 month of age with narrower proposed therapeutic indications than the current Losec PI (indicated for children > 1 year). Zollinger-Ellison was removed as an indication.

Confirmation of the suitability of the COR evaluated paediatric data was also obtained, which included a Pharmacodynamic (PD)/efficacy study in infants (Study DA 04/07) plus a Pharmacokinetic (PK) study which bridges efficacy/safety data. No Risk Management Plan was required for this submission.

The proposed additional drug substance manufacturing site will be approved by a post-approval application.

The following TGA guidelines are considered relevant to this submission:

- Australian Regulatory Guidelines for Prescription Medicines <https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm>
- Form for providing product information <https://www.tga.gov.au/form-providing-product-information>

The following international guidelines are considered relevant to this submission:

- EMA guideline on clinical investigation of medicinal products in the paediatric population [E11\(R1\) Step 5 Clinical investigation of medicinal products in the paediatric population \(europa.eu\)](https://www.ema.europa.eu/en/clinical-investigation-guidelines)

3.4. Evaluator's commentary on the background information

The background information is satisfactory.

4. Contents of the clinical dossier

Section	Page reference in COR report	Acceptable?
Scope of the clinical dossier	13 – 25	Yes ☒ No ☐
Paediatric data	16 – 17, 21 - 23	Yes ☒ No ☐
Good clinical practice	9	Yes ☒ No ☐

4.1.1. Scope of the clinical dossier

Table 1 provides an overview of the clinical studies supporting registration evaluated in the COR evaluation report:

Table 1 Tabular listing of all clinical studies

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4.2. Evaluator's commentary on the clinical dossier

The clinical dossier is satisfactory. This evaluation is based on the COR assessment reports provided in Module 1.11.4. Module 2 summaries were referred to.

5. Pharmacokinetics

Section	Page reference in COR report	Acceptable?
Studies providing pharmacokinetic information	14 - 15, 17 -18	Yes ☒ No ☐
Summary of pharmacokinetics	14 – 15, 18 -19	Yes ☒ No ☐
Physicochemical characteristics of the active substance	N/A	Yes ☐ No ☐

Pharmacokinetics in healthy subjects: <ul style="list-style-type: none"> • Absorption • Bioavailability • Distribution • Metabolism • Excretion 	17	Yes ☒ No ☐
Intra and inter individual variability of pharmacokinetics	N/A	Yes ☐ No ☐
Pharmacokinetics in the target population	17	Yes ☒ No ☐
Pharmacokinetics in special populations <ul style="list-style-type: none"> • Pharmacokinetics in subjects with impaired hepatic function • Pharmacokinetics in subjects with impaired renal function • Pharmacokinetics according to age • Pharmacokinetics related to genetic factors • Pharmacokinetics in other special population / with other population characteristic 	N/A	Yes ☐ No ☐
Population pharmacokinetics	17	Yes ☒ No ☐
Pharmacokinetic interactions	N/A	Yes ☐ No ☐
Clinical implications of in vitro findings	N/A	Yes ☐ No ☐

5.1.1. Bioavailability/bioequivalence

s47

s47



5.1.2. Population PK model

s47



5.2. Evaluator's overall conclusions on pharmacokinetics

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6. Pharmacodynamics

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Studies providing pharmacodynamic information	15 - 19	Yes ☒ No ☐ See additional information below.
Summary of pharmacodynamics <ul style="list-style-type: none"> • Mechanism of action • Pharmacodynamic effects (primary and secondary) • Time course of pharmacodynamic effects • Relationship between drug concentration and pharmacodynamic effects • Genetic, gender and age related differences in pharmacodynamic response • Pharmacodynamic interactions 	16 - 19	Yes ☒ No ☐

6.1.1. Study BA 04/07: supportive pharmacodynamic/ safety/efficacy paediatric study

s47

6.2. Evaluator's overall conclusions on pharmacodynamics

s47

7. Dosage selection for the pivotal studies

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Pharmacokinetics and pharmacodynamics: dose finding studies	17	Yes ☐ No ☐
Phase II dose finding studies	N/A	Yes ☐ No ☐
Phase III pivotal studies investigating more than one dose regimen	N/A	Yes ☐ No ☐

7.1. Evaluator's conclusions on dose finding for the pivotal studies

See Section 5.2 and 6.2.

8. Clinical efficacy

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Studies providing evaluable efficacy data	16	Yes ☒ No ☐
Pivotal or main efficacy studies	16	Yes ☒ No ☐
Phase III pivotal studies investigating more than one dose regimen	N/A	Yes ☐ No ☐
Other efficacy studies	N/A	Yes ☐ No ☐

Analyses performed across trials: pooled and meta analyses	N/A	Yes ☐ No ☐
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8.1. Evaluator's conclusions on clinical efficacy

See Section 6.2.

9. Clinical safety

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
<p>Studies providing evaluable safety data:</p> <ul style="list-style-type: none"> Pivotal studies that assessed safety as the sole primary outcome Pivotal and/or main efficacy studies Other studies: <ul style="list-style-type: none"> Studies with evaluable safety data: dose finding and pharmacology Studies evaluable for safety only 	<p>N/A</p> <p>21 -23</p> <p>20, 21</p>	<p>Yes ☒ No ☐</p>
Studies that assessed safety as the sole primary outcome	N/A	Yes ☐ No ☐
Patient exposure	19	Yes ☒ No ☐
<p>Adverse events:</p> <ul style="list-style-type: none"> All adverse events (irrespective of relationship to study treatment) Treatment related adverse events (adverse drug reactions) Deaths and other serious adverse events 	19, 22	Yes ☒ No ☐

- | | | |
|--|--|--|
| <ul style="list-style-type: none"> Discontinuations due to adverse events | | |
|--|--|--|

9.1.1. Oral suspension safety data

s47

9.1.2. Paediatric safety data evaluation

s47

9.2. Adverse events not included in COR assessment

N/A

9.3. Evaluation of issues with possible regulatory impact

Section	Page reference in COR report	Acceptable? If no, include comments as annotations in COR report
Liver function and liver toxicity	N/A	Yes ☐ No ☐
Renal function and renal toxicity	N/A	Yes ☐ No ☐
Other clinical chemistry	N/A	Yes ☐ No ☐
Haematology and haematological toxicity	N/A	Yes ☐ No ☐
Other laboratory tests	N/A	Yes ☐ No ☐

² Summary on page 446 -449 of [e006329 \(0000-\) - 5.4 Literature References - Common](#)

³ Article p 781 of [e006329 \(0000-\) - 5.4 Literature References - Common](#); Characteristics of Children Receiving Proton Pump Inhibitors Continuously for Up to 11 Years Duration Hassal E, Kerr W., Hashem B Journal of Pediatrics V150, 2007 p 262-267

Electrocardiograph findings and cardiovascular safety	N/A	Yes ☐ No ☐
Vital signs and clinical examination findings	N/A	Yes ☐ No ☐
Immunogenicity and immunological events	N/A	Yes ☐ No ☐
Serious skin reactions	N/A	Yes ☐ No ☐
Other safety parameters	N/A	Yes ☐ No ☐
Other safety issues	N/A	Yes ☐ No ☐
Post marketing experience	N/A	Yes ☐ No ☐

9.4. Post marketing experience not assessed by COR report

N/A

9.5. Evaluator's overall conclusions on clinical safety

S47



10. First round benefit-risk assessment

10.1. First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Oral suspension omeprazole provides an alternative route of administration for the treatment of reflux in paediatric and adult patients.	Currently available omeprazole requires suspension of granules prior to use and administration by caregivers as a liquid.
The oral suspension formulation enables more accurate dosing, particularly in patients under 10 kg requiring doses below 10 mg.	
s47	s47

10.2. First round assessment of risks

Risks	Strengths and Uncertainties
s47	s47

10.3. First round assessment of benefit-risk balance

s47

11. First round recommendation regarding authorisation

At this stage there is no clinical objection to registration of PediPPI omeprazole oral suspension 2mg/mL and 4mg/mL subject to satisfactory response to the Clinical questions.

12. First round comments on product documentation

The following comments relate to the proposed PediPPI PI provided in Module 1.3, Sequence 0000 ([e006329 \(0000-\) - 1.3.1.2 Product information - annotated - 0000](#)).

As per the comments in Section 2.2, the PI for PediPPI Omeprazole Powder for oral suspension, is new. It is based on the Australian Losec PI ([Local Product Information - Australia \(tga.gov.au\)](#)) using the EU SmPC ([e006329 \(0000-\) - 1.11.2 Foreign product information](#)) for indications and instructions relevant to the oral suspension formulation and paediatric dosing.

There are also additions to the PI proposed in line with the current NZ Data Sheet of Losec ([e006329 \(0000-\) - 1.11.2 Foreign product information](#)).

12.1. First round comments on draft PI (clinical aspects)

Proposed
<p>4.1 Therapeutic indications</p> <p><u>Adults</u></p> <ul style="list-style-type: none"> ▪ Treatment of duodenal ulcers ▪ Prevention of relapse of duodenal ulcers ▪ Treatment of gastric ulcers ▪ Prevention of relapse of gastric ulcers ▪ In combination with appropriate antibiotics, <i>Helicobacter pylori</i> (<i>H. pylori</i>) eradication in peptic ulcer disease ▪ Treatment of NSAID-associated gastric and duodenal ulcers ▪ Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk ▪ Treatment of reflux oesophagitis ▪ Long-term management of patients with healed reflux oesophagitis ▪ Treatment of symptomatic gastro-oesophageal reflux disease (GORD) <p><u>Paediatric use</u></p> <p><u>Children over 1 month of age</u></p> <ul style="list-style-type: none"> ▪ Treatment of reflux oesophagitis ▪ Symptomatic treatment of heartburn and acid regurgitation in GORD <p><u>Children over 4 years of age and adolescents</u></p> <p>In combination with antibiotics in treatment of duodenal ulcer caused by <i>H. pylori</i></p> <p>P2</p> <p>Section 4.1 aligns with the EU SmPC.</p>

The wording differs from the current Australian Losec PI, but the conditions for which it is indicated to treat and prevent relapse remain the same, with the exception of Zollinger Ellison syndrome.

The Sponsor indicated a large volume of omeprazole oral suspension would be required to achieve treatment doses (60 mg omeprazole daily initially titrated up or down) and the bottle size (2mg/mL: total bottle 180 mg of omeprazole; 4mg/mL: total bottle 360 mg) does not cater for the volumes required. The 4 mg/mL bottle would last 6 doses at 60 mL each dose.

The indications for paediatric use are aligned with the EU SmPC. The current Losec PI does not include separate therapeutic indications for paediatric patients. Guidance use in paediatric patients from 1 year is provided in the Section 4.2 Dose and Method of Administration.

The rationale for not including Zollinger Ellison as an indication is acceptable. Alternative treatment options are available to better cater for the required high dose.

*The wording for the indications of gastric and duodenal ulcers, treatment of *H. pylori*, NSAID associated gastric and duodenal ulcers, reflux oesophagitis and gastro-oesophageal reflux disease is in line with the current Losec PI, is clear, and is accepted.*

The paediatric indications are acceptable for the Australian PI.

Proposed

4.2 Dose and method of administration

PediPPI is recommended to be given in the morning.

Commented [529]: Added in line with Losec NZ Data Sheet

PediPPI 2 mg/mL oral suspension is suitable for doses of ≤ 15 mg. For doses of 20 mg or greater, PediPPI 4 mg/mL oral suspension is suitable.

Commented [530]: Added in line with PEDIPPI SmPC, as specific for suspension dosage form

P3

The advice on dosing in the morning is not present in the current Losec PI or EU SmPC but is based on the NZ data sheet. Indication has not been provided as to why this was required in NZ.

Indication as to why a morning dose was a requirement in the NZ DS will need to be provided by the Sponsor (see Clinical questions Section 13.1).

The advice on the available suspension forms and suitability based on target dose, as per the EU SmPC, is accepted.

Zollinger-Ellison Syndrome

Recommended initial dose: omeprazole 60 mg once daily.

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

Use in children

Children over 1 month of age

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in GORD

Age	Weight	Dose*
1 month to 1 year of age	--	1 mg/kg once daily. Doses above 1.5 mg/kg/day have not been studied.
≥ 1 year of age	10 - 20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed.

* Individual dose measurements ≤ 2 mL of the 2 mg/mL presentation are not indicated.

The 2 mg/mL and 4 mg/mL strengths are equivalent with respect to buffering capacity (same amount of buffer on a mL basis).

For doses of ≤ 15 mg, the 2 mg/mL strength is recommended. The 2 mg/mL strength is indicated for age 1 month to 1 year for administering up to 15 mg, and ≥ 1 year of age for administering 10 mg, to provide sufficient buffering capacity and absorption.

For doses of 20 mg or 40 mg, the 4 mg/mL strength is suitable. The 4 mg/mL strength is indicated for administration of 20 mg or 40 mg so that a maximum of 2 doses are required.

Reflux oesophagitis: The treatment time is 4 - 8 weeks.

Commented §29.10: Dosage information for Zollinger-Ellison syndrome, present in the approved Product Information for Losec Tablets, has been removed as this indication is not included in the approved PEDIPPI SmPC and consequently not proposed for the AU PI for PedIPPI.

Please also refer to the DIRECTIONS FOR EVALUATORS TO THE EVIDENCE BASE FOR THIS PI on the cover page for this PI regarding the indication of Zollinger-Ellison Syndrome.

Commented §29.10: This entire sub-section is included in line with the approved PEDIPPI SmPC.

Commented §29.11: Note for information: The dosage for children over 1 year of age is identical to the approved dosage in Losec Tablets AU PI.

Commented §29.12: Please note this statement is specific to the 2 mg/mL strength and only included in the approved PEDIPPI SPC for the 2 mg/mL strength. It is not included in the approved PEDIPPI SPC for the 4 mg/mL strength. Since the PI covers information for both strengths, the words "of the 2 mg/mL presentation" have been added to the statement to ensure the information is attributed to the correct strength.

P5

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease: The treatment time is 2 - 4 weeks. If symptom control has not been achieved after 2 - 4 weeks the patient should be investigated further.

Children over 4 years of age and adolescents

- Treatment of duodenal ulcer caused by *H. pylori*

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

Weight	Dose
15 - 30 kg	Combination with two antibiotics: omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together two times daily for one week.
31 - 40 kg	Combination with two antibiotics: omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered two times daily for one week.
> 40 kg	Combination with two antibiotics: omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered two times daily for one week.

Elderly

No dosage adjustment of omeprazole is necessary in the elderly.

Hepatic impairment

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

Renal impairment

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

Commented §29.31: As noted above, the *Use in children* section is based on the approved PEDIPPI SPC, and proposed to be included in the AU PI as a consequence of including the corresponding paediatric indication as per the approved PEDIPPI SPC.

In addition for this particular sub-section, the sponsor proposes to further amend the present proposed dosage information for Australia by removing the specific names and dosage for the antibiotics mentioned in the SPC, as no such indication and/or dosage is contained in the AU Losec tablets PI dated 09 March 2021, the AU Klocid PI dated 18 September 2019 or the Amoxal PI dated 06 May 2022.

However, it is of note that this dosage information is included in the UK SPC for Losec Capsules 20 mg, MA holder AstraZeneca UK Ltd, dated 19 May 2017 (please refer to Module 1.11.2).

Method of administration

Omeprazole oral suspension should be taken on an empty stomach, at least 30 minutes before a meal.

Precautions to be taken before handling or administering the medicinal product

Omeprazole powder for oral suspension requires reconstitution prior to oral administration. For instructions on reconstitution of the medicinal product before administration, see Section 6.6. Special precautions for disposal.

For instructions for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes (see Section 6.6. Special precautions for disposal).

Commented [522, 4]: All text under this heading is taken from the approved PED/PP1 SmPC as it is specific for suspension dosage form.

P6

The discussion of removal of advice on Zollinger-Ellison Syndrome is discussed above.

The prescribing advice for use in children aligns with the EU SmP. The prescribing advice for treatment of *H. pylori* aligns with the Losec PI.

Method of administration aligns with the Eu SmPC.

The proposed prescribing advice for children is accepted as is the method of administration.

Proposed

4.4 Special warnings and precautions for use

Hypomagnesaemia

Symptomatic hypomagnesaemia has been reported rarely in patients treated with long-term PPI medication. In some severe cases hypocalcaemia was also reported. Severe hypomagnesaemia may result in serious adverse events such as tetany, seizures and potentially also arrhythmias. In some patients, treatment of hypomagnesaemia with magnesium replacement was not sufficient to correct the magnesium imbalance and discontinuation of the PPI was required. In patients later retreated with the same or different PPI, hypomagnesaemia returned within a shorter time period. For patients expected to be on prolonged treatment or who take PPIs with other medicines such as digoxin or medicines that may cause hypomagnesaemia, consideration should be given to monitoring magnesium levels prior to initiation and periodically thereafter.

Use in hepatic impairment

Commented [522, 5]: This section is additional and was added based on NZ DS of Losec, and is also in line with approved SmPC of PED/PP1. AU PI for Losec tablets also mentions this, but in the AE section.

P8

Inclusion of hypomagnesaemia in this section to align with the NZ DS is acceptable.

Proposed

4.5 Interactions with other medicines and other forms of interactions

Citalopram / Escitalopram

Co-administration of omeprazole (20 mg) with citalopram (20 mg single dose) doubles the AUC of the S-isomer of citalopram, but the R-isomer of citalopram is not affected. A reduction in the dose of citalopram may be necessary based on clinical judgement. For patients taking omeprazole, the citalopram dose should not exceed the maximum dose of 20 mg/day.

Co-administration of omeprazole (30 mg) with escitalopram (20 mg single dose) increased the plasma levels (approximately 50%) and terminal half-life (31%) of escitalopram. A reduction in the dose of escitalopram may be necessary based on clinical judgement.

Effects of other drugs on omeprazole

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

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

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

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

Potential interactions that have been excluded

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

Commented [522]: Proposed to be added in line with NZ DS of Losec.

Commented [522]: Proposed to be added in line with NZ DS of Losec.

P11

Inclusion of the paragraph on citalopram/ escitalopram interaction and addition of 2 medications that do not interact with omeprazole are proposed to align with the NZ DS.

Indication as to why these differences are present in the NZ DS will need to be provided by the Sponsor (see Clinical questions Section 13).

Proposed

4.6 Fertility, Pregnancy and Lactation

Use in pregnancy (Category B3)

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

Commented [522]: In line with approved AU PI for Losec tablets

P12

Use in pregnancy category of B3 is accepted.

Proposed

4.8 Adverse effects (undesirable effects)

Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

Reporting suspected adverse effects

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

Commented ⁵²²[19]: This section is relevant information on adverse effects applicable to the extended paediatric population as per the approved PEDIPPI SmPC and is therefore proposed for inclusion in the PI.

P14

Inclusion of the paragraph on safety in the paediatric population aligns with the EU SmPC and is accepted.

Proposed

5.1 Pharmacodynamic properties

In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90% of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0 – 24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of the dose.

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

Commented ⁵²²[20]: This information is related to the extended paediatric population and is proposed in line with the approved PEDIPPI SmPC.

P17

Inclusion of the paragraph on pharmacodynamic properties in the paediatric population aligns with the EU SmPC and is accepted.

Proposed

5.2 Pharmacokinetic properties

Absorption

Omeprazole is acid labile and is therefore administered in omeprazole oral suspension as a buffered suspension. The buffer protects omeprazole from acid degradation, facilitating absorption.

Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 30 minutes after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3 - 6 hours. In a bioavailability study, the administration with food (milk) reduced the extent of absorption by approximately 20%. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Commented ^{s221}: Absorption section proposed in line with PEDIPPI SmPC as related to the oral suspension dosage form

Distribution

P17

In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

Commented ^{s222}: This information is related to the extended paediatric population and is included in line with the approved PEDIPPI SmPC.

P18

Inclusion of the paragraph on pharmacokinetic properties in the paediatric population aligns with the EU SmPC and is accepted.

12.2. First round comments on draft CMI (clinical aspects)

The Sponsor included a CMI in Module 1.3.2.1 ([e006329 \(0000-\) - 1.3.2.1 Consumer medicines information - clean - 0000](#)). This is a new CMI proposed for Australia and New Zealand.

The CMI was acceptable. Inclusion of citalopram/escitalopram as an interaction was noted and is accepted pending provision of the relevant clinical information (See Section 13).

12.3. First round comments on draft RMP (Summary of Safety Concerns)

No Risk Management Plan was required for this submission.

13. Clinical questions

13.1. PI and CMI

s47

14. First round evaluation errata

There were no Errors or Omissions raised by the Sponsor.

15. Second round evaluation

Note was made of a change in the trade name to ***Omeprazole ADVZ***. The product will be referred to as Omeprazole ADVZ in the remainder of this report.

The Sponsor provided an update that the PI has been revised in line with the latest updated PI of Australian innovator product: Losec tablets dated 21 November 2022.

These changes update the safety warning on hypomagnesaemia and are accepted. They are summarised in Section 18.

15.1. Response to Clinical Questions

s47



16. Second round benefit-risk assessment

There is no change to the benefit-risk assessment.

17. Second round recommendation regarding authorisation

Based on the evaluation of the clinical data, and the sponsor's response to the first-round evaluation, the evaluator recommends approval of Omeprazole Powder for oral suspension.

18. Second round comments on product documentation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Omeprazole ADVZ 2 mg/mL powder for oral suspension: After reconstitution, each 1 mL of suspension contains 2 mg of omeprazole. Each reconstituted bottle (90 mL) contains 180 mg of omeprazole.

Omeprazole ADVZ 4 mg/mL powder for oral suspension: After reconstitution, each 1 mL of suspension contains 4 mg of omeprazole. Each reconstituted bottle (90 mL) contains 360 mg of omeprazole.

Excipients with known effect:

Each 1 mL of suspension contains sodium methyl hydroxybenzoate 2.3 mg, maltitol 272 mg, sodium benzoate 5 mg, sodium 17.2 mg and potassium 54.3 mg.

For the full list of excipients, see Section 6.1 List of excipients.

Commented §222: Changed as per the AAN name of the ingredients.

Additions to the PI I line proposed to align with the Losec PI.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Severe hypomagnesaemia may result in serious adverse events such as tetany, seizures and potentially also arrhythmias. In some patients, treatment of hypomagnesaemia with magnesium replacement was not sufficient to correct the magnesium imbalance and discontinuation of the PPI was required. In patients later retreated with the same or different PPI, hypomagnesaemia returned within a shorter time period. For patients expected to be on prolonged treatment or who take PPIs with other medicines such as digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), consideration should be given to monitoring magnesium levels prior to initiation and periodically thereafter.

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

Commented §223: Revised in line with the AU innovator Losec tablets dated 21 November 2022.

Commented §224: Revised in line with the AU innovator Losec tablets dated 21 November 2022.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children)..

Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Commented §225: Revised in line with the AU innovator Losec tablets dated 21 November 2022.

All additions are accepted.

19. References

N/A

20. Supporting information, tables and figures

N/A

21. Attachment: additional evaluation material

N/A

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