Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Omeprazole 10 mg oral solution
Omeprazole 20 mg oral solution

omeprazole

PL 25258/0382-0383

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Omeprazole 10 mg and 20 mg oral solution
omeprazole

This is a summary of the Public Assessment Report (PAR) for Omeprazole 10 mg and 20 mg oral solution. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Omeprazole oral solution in this lay summary for ease of reading.

For practical information about using Omeprazole oral solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Omeprazole oral solution and what is it used for?
Omeprazole 10 mg and 20 mg oral solution are hybrid medicines. This means that the medicines are similar to a reference medicine already authorised, called Losec hard gastro-resistant 20 mg capsules (PL 45043/0101) albeit with certain differences. In this case, Omeprazole 10 mg and 20 mg oral solution are a different strength and pharmaceutical form to the reference product.

Omeprazole oral solution is used in the treatment to treat the following conditions:
In adults:

- 'Gastro-oesophageal reflux disease' (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects the throat to the stomach) causing pain, inflammation and heartburn.
- Ulcers in the upper part of the intestine (duodenal ulcer) or stomach (gastric ulcer).
- Ulcers which are infected with bacteria called '*Helicobacter pylori*'. For this condition, the patient's doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Ulcers caused by medicines called NSAIDs (Non-Steroidal Anti- Inflammatory Drugs). Omeprazole oral solution can also be used to stop ulcers from forming in patients that are taking NSAIDs.

In children:
Children over 1 year of age and ≥ 10 kg
'Gastro-oesophageal reflux disease' (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects the throat to the stomach) causing pain, inflammation and heartburn.
In children, the symptoms of the condition can include the return of stomach contents into the mouth (regurgitation), being sick (vomiting) and poor weight gain.

Children and adolescents over 4 years of age
Ulcers which are infected with bacteria called '*Helicobacter pylori'*. If the child has this condition, their doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

How does Omeprazole oral solution work?
Omeprazole oral solution contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that the stomach produces.

How is Omeprazole oral solution used?
The pharmaceutical form of these medicines is an oral solution and the route of administration is oral (by mouth).

The patients' doctor will tell them how much solution to take and how long to take it for. This will depend on the patients' condition and how old they are.

Recommended Dose
Use in adults
To treat symptoms of GORD such as heartburn and acid regurgitation:
- If the patients' doctor has found that the food pipe (gullet) has been slightly damaged, the recommended dose is 20 mg once a day for 4-8 weeks. The doctor may tell their patient to take a dose of 40 mg for a further 8 weeks if the gullet has not yet healed.
- The recommended dose once the gullet has healed is 10 mg once a day.
- If the gullet has not been damaged, the usual dose is 10 mg once a day.

To treat ulcers in the upper part of the intestine (duodenal ulcer):
- The recommended dose is 20 mg once a day for 2 weeks. The doctor may tell their patient to take the same dose for a further 2 weeks if the ulcer has not yet healed.
- If the ulcers do not fully heal, the dose can be increased to 40 mg once a day for 4 weeks.

To treat ulcers in the stomach (gastric ulcer):
- The recommended dose is 20 mg once a day for 4 weeks. The doctor may tell their patient to take the same dose for a further 4 weeks if their ulcer has not yet healed.
- If the ulcers do not fully heal, the dose can be increased to 40 mg once a day for 8 weeks.

To prevent the duodenal and stomach ulcers from coming back:
- The recommended dose is 10 mg or 20 mg once a day. The doctor may increase the dose to 40 mg once a day.

To treat duodenal and stomach ulcers caused by NSAIDs (Non- Steroidal Anti-Inflammatory Drugs):
- The recommended dose is 20 mg once a day for 4 to 8 weeks.

To prevent duodenal and stomach ulcers if the patient is taking NSAIDs:
- The recommended dose is 20 mg once a day.

To treat ulcers caused by *Helicobacter pylori* infection and to stop them coming back:
- The recommended dose is 20 mg Omeprazole oral solution twice a day for one week.
- The doctor will also tell their patient to take two antibiotics among amoxicillin, clarithromycin and metronidazole.

Use in children and adolescents

To treat symptoms of GORD such as heartburn and acid regurgitation:

- Children over 1 year of age and with a body weight of more than 10 kg may take Omeprazole oral solution. The dose for children is based on the child's weight and the doctor will decide the correct dose.

To treat ulcers caused by *Helicobacter pylori* infection and to stop them coming back:

- Children aged over 4 years may take Omeprazole oral solution. The dose for children is based on the child's weight and the doctor will decide the correct dose.
- The doctor will also prescribe two antibiotics called amoxicillin and clarithromycin for the child.

Taking this medicine

- It is recommended that the patient take this medicine in the morning.
- This medicine should be taken on an empty stomach, at least 1 hour before a meal. 10 mg and 20 mg strengths are equivalent with to buffering capacity (same amount of buffer on a ml basis). To achieve a 40 mg dose Omeprazole 20 mg oral solution should be used.
- This medicine can also be administered via nasogastric (NG) or percutaneous endoscopic gastronomy (PED) tubes. For further information about this, please refer to the PIL.

For further information on how Omeprazole oral solution is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Omeprazole oral solution has been shown in studies?

Omeprazole oral solution is a hybrid medicine, studies in healthy volunteers consist of tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Omeprazole oral solution?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Omeprazole oral solution is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why was Omeprazole oral solution approved?
Omeprazole oral solution has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Omeprazole oral solution?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Omeprazole oral solution. The RMP details the important risks of Omeprazole oral solution, how these risks can be minimised, any uncertainties about Omeprazole oral solution (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Omeprazole oral solution:

Important identified risk(s)	• None
Important potential risk(s)	• Hyperkalaemia • Risk of masking symptoms of more serious conditions (e.g gastrointestinal cancer) • Gastrointestinal effects/infections related to acid inhibition • Severe cutaneous reactions
Missing information	• Long-term treatment with omeprazole in children (with GERD)

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Omeprazole oral solution are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided for these products and are satisfactory.

Other information about Omeprazole oral solution
Marketing Authorisations for Omeprazole oral solution were granted in the United Kingdom (UK) on 31 August 2023.

The full PAR for Omeprazole oral solution follows this summary.

This summary was last updated in November 2023.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Omeprazole 10 mg and 20 mg oral solution(PL 25258/0382-0383) could be approved.

The products are approved for the following indications:
Adults

- 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, *Helicobacter pylori (H. pylori)* 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

Paediatric use
Children over 1 year of age and ≥ 10 kg

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

Children and adolescents over 4 years of age

- In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H + K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

These applications were approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be hybrid medicinal products of a suitable originator product, Losec hard gastro-resistant 20 mg capsules, that has been licensed for suitable time, in line with the legal requirements.

Data from bioequivalence study (AKD-P5-352) were submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 07 April 2022. The Commission was of the provisional opinion that that on grounds relating to quality, safety and efficacy it may be unable to advice the MHRA to grant the Marketing authorisations for the products. Following consideration of the applicant's written response on 27-28 April 2023, the CHM advised the grant of the marketing authorisations for the products, subject to resolution of the outstanding points.

National marketing authorisations were granted in the United Kingdom (UK) on 31 August 2023.

II QUALITY ASPECTS

II.1 Introduction

The active substance is omeprazole.
One bottle of the constituted Omeprazole 10 mg oral solution (entire bottle content – 15 mL) contains 10 mg of omeprazole.
One bottle of constituted Omeprazole 20 mg oral solution (entire bottle content – 15 mL) contains 20 mg of omeprazole.

The other ingredients are: glycerol (E422), xanthan gum (E415), sodium carboxymethylcellulose (E468), sucralose (E955), emulsion simethicone 30%, sodium hydrogen carbonate, sodium dihydrogen phosphate dehydrate, domiphen bromide, polysorbate 80 (E433), disodium edetate, N-acetyl L cysteine, sodium hydroxide (E524), nitrogen, menthol flavour (consisting of acacia gum (E414), flavouring components), taste masking flavour (consisting of water, propylene glycol (E1520), flavouring components), lemon flavour (for 20mg) (consisting of maize maltodextrin, flavouring components).

The finished products are packaged in a cardboard box containing 14 single-dose dual-chamber HDPE (high density polyethylene) bottles located on PVC (polyvinyl chloride) saucer.

The dual-chamber primary packaging for Omeprazole 10 mg (15 ml) is composed of assembled:

- HDPE (high density polyethylene) Cap with tamper evident ring, with PP (polypropylene) plunger and PE (polyethylene) membrane filled with 5 ml of Omeprazole 2 mg/ml solution.

HDPE (high density polyethylene) Bottle filled with 10 ml of diluent
The dual-chamber primary packaging for Omeprazole 20 mg (15 ml) is composed of assembled:

- HDPE (high density polyethylene) Cap with tamper evident ring, with PP (polypropylene) plunger and PE (polyethylene) membrane filled with 5 ml of Omeprazole 4 mg/ml solution.
- HDPE (high density polyethylene) Bottle with neck filled with 10 ml of diluent for Omeprazole 20 mg oral solution.

The concentrated solution in the cap and the diluent in the bottle are mixed when the container is opened.

Not all pack sizes may be marketed.

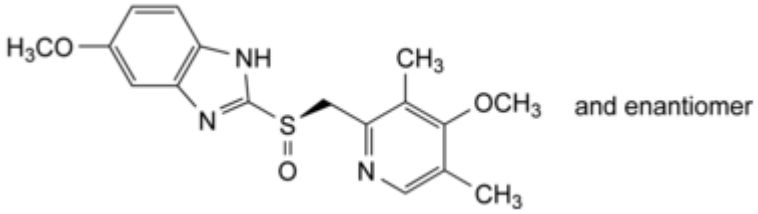
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: omeprazole

Chemical Name: 5-Methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2 yl)methyl]sulfinyl]-1*H*-benzimidazole.

Molecular Formula: $C_{17}H_{19}N_3O_3S$



Chemical Structure:

Molecular Weight: 345.4

Appearance: White or almost white powder.

Solubility: Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

Omeprazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national pharmacopoeia monographs, or suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions 'store in a refrigerator (2°C – 8°C) and store in the original package to protect from light', is acceptable.

The products are stable for up to 28 days if unopened and kept at room temperature (15°C - 25°C).

The product should be taken within 20 minutes of opening the container and mixing the concentrated solution and diluent. During this time, it should be kept out of the sight and reach of children.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these are hybrid applications of an already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from a bioequivalence study (AKD-P5-352) have been submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following.

STUDY 1: AKD-P5-352

This study was a single centre, randomized, single-dose, laboratory-blinded, 3-treatment, 3-period, 6-sequence, crossover study under fasting conditions, with a 7-day wash-out between treatments. It was conducted in 42 healthy male and female subjects. The rate and extent of absorption of omeprazole were measured and compared following a single dose administration of the Investigational Medicinal Products: Treatment-1 (2 x 15 mL of 10 mg/15 mL), Treatment-2 (1 x 15 mL of 20 mg/15 mL) and Reference Medicinal Product (Treatment-3 1 x 20 mg hard gastro-resistant capsule). To evaluate study drug pharmacokinetics, blood samples were collected through 12 hours after dosing.

A summary of the pharmacokinetic results are presented below:

Parameters	Geometric mean ratio (90% CI)	ISCV (%)
Omeprazole		
Tmax(h)	NA	NA
Cmax(ng/mL)	178.40 (160.58-198.19)	28.8
AUC0-T(ng h/mL)	111.28 (104.84-118.12)	16.1
Parameters	**Geometric mean ratio (90% CI)**	**ISCV (%)**
Omeprazole		
Tmax(h)	NA	NA
Cmax(ng/mL)	174.99 (153.30-199.76)	37.2
AUC0-T(ng h/mL)	109.09 (101.57-117.18)	19.6
Parameters	**Geometric mean ratio (90% CI)**	**ISCV (%)**
Omeprazole		
Tmax(h)	NA	NA
Cmax(ng/mL)	102.19 (91.38-114.27)	30.7
AUC0-T(ng h/mL)	102.09 (95.07-109.62)	19.3

Abbreviations: ISCV = intra-subject coefficient of variation, NA=not applicable.
a. Data are presented as mean ± standard deviation (SD) except for Tmax, for which median (minimum – maximum) is presented.

The Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test products and the reference product for the AUC, but not for the Cmax, as the 90% confidence intervals for Cmax were outside the acceptable range.

The applicant subsequently provided suitable justification for the lack of relevance for efficacy of the higher Cmax. Implications for exposure on multiple dosing were additionally discussed and the difference in Cmax was also considered in terms of potential drug-drug interactions. This was therefore accepted.

Suitable justification was also provided for the absence of a bioequivalance study under fed conditions.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the products.

The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPCs and PIL for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**