

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1463/021/001

Case No: 2078590

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

IMED Healthcare Ltd.

New Road, Buncrana, Co. Donegal, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Losec MUPS 10mg Gastro-Resistant Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/03/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Losec MUPS 10mg Gastro-Resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10.3mg omeprazole magnesium, equivalent to 10mg omeprazole, as coated pellets.

Excipient: Sucrose (contained in sugar spheres)

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant, film-coated Tablets.

Product imported from the UK:

Light-pink, oblong, biconvex tablets engraved with a logo on one side and '10mg' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of oesophageal reflux disease, including reflux oesophagitis.

Treatment of duodenal and benign gastric ulcers.

Healing and prophylaxis of NSAID-associated benign gastric ulcers and duodenal ulcers.

Helicobacter pylori eradication in peptic ulcer disease. Relief of associated dyspeptic symptoms.

Prophylaxis of acid aspiration.

Zollinger-Ellison syndrome.

Children over 1 year of age and ≥ 10 kg: Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

4.2 Posology and method of administration

Adults only

Oesophageal reflux disease: For oesophageal reflux disease the usual dose is 20 mg Losec MUPS once daily. In reflux oesophagitis, the majority of patients are healed after 4 weeks. For those patients not fully healed after the initial course, healing usually occurs during a further 4-8 weeks treatment.

Losec MUPS has also been used at a dose of 40 mg once daily in patients with reflux oesophagitis refractory to other therapy. Healing usually occurs within 8 weeks.

Acid reflux disease: For long-term management, Losec MUPS 10 mg once daily is recommended, increasing to 20 mg if symptoms return.

Duodenal and benign gastric ulcers: The usual dose is 20 mg Losec MUPS once daily. The majority of patients are healed after 4-8 weeks. In severe cases, the dose may be increased to 40 mg once daily.

Maintenance treatment: For prevention of relapse in patients with duodenal ulcer the recommended dose is Losec MUPS 10 mg once daily, increasing to 20 mg once daily if symptoms return. The following groups are at risk from recurrent ulcer relapse: Younger patients (<60 years), those whose symptoms persist for more than 1 year and smokers. These patients will require long-term therapy with Losec MUPS 20 mg once daily, reducing to 10 mg once daily, if possible.

The recommended dosage is 20 mg Losec MUPS once daily for the prevention of relapse in patients with severe reflux oesophagitis or poorly responsive peptic ulcer.

If recurrence occurs, the dose can be increased to 40 mg Losec MUPS once daily. As a matter of good clinical practice, patients requiring long-term maintenance treatment should be reviewed periodically by the physician

Healing and prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers: For the healing of NSAID-associated gastric ulcers and duodenal ulcers, the recommended dosage of Losec MUPS is 20 mg once daily. The effectiveness of Losec MUPS is not affected by concomitant NSAID treatment. In most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 week treatment.

For the prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers, the recommended dosage of Losec MUPS is 20 mg once daily.

***Helicobacter pylori* (Hp) eradication regimens in peptic ulcer disease:** Losec MUPS is recommended at a dose of 20 mg twice daily in association with antimicrobial agents as detailed below:

Triple therapy regimens:

Losec MUPS and the following antimicrobial combinations:

Clarithromycin 250 mg and metronidazole 400 mg both twice a day for one week.

Or

Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week.

Dual therapy regimens:

Losec MUPS 20 mg twice daily with oral Amoxicillin 1 g twice daily for two weeks. Alternatively Losec MUPS 40 mg once daily and clarithromycin 500 mg three times a day for two weeks.

In each regimen if symptoms return and the patient is *Hp* positive therapy may be repeated or one of the alternative regimens can be used; if the patient is *Hp* negative then see dosage instruction for acid reflux disease.

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

Prophylaxis of acid aspiration: For patients considered to be at risk of aspiration of the gastric contents during general anaesthesia, the recommended dosage is Losec MUPS 40 mg on the evening before surgery followed by Losec MUPS 40 mg 2-6 hours prior to surgery.

Zollinger-Ellison syndrome: The usual initial dose is 60 mg Losec MUPS with subsequent adjustment to achieve optimal response in the range of 20-120 mg daily. Doses above 80 mg should be given as a twice daily regimen. Treatment should be continued under specialist supervision as long as clinically indicated.

Elderly: Dosage adjustment is not necessary.

Children:**Reflux oesophagitis**

The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal 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.

The dosage recommendations are as follows:

Age	Weight	Dosage
≥ 1 year of age	10-20 kg	10 mg once daily. The dosage can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dosage can be increased to 40 mg once daily if needed.

Children over 4 years of age

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

When selecting appropriate combination therapy consideration should be given to official 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	Dosage
15-≤ 30 kg	Combination with two antibiotics: Losec Mups 10 mg, amoxicillin 25 mg/kg body Weight and clarithromycin 7.5 mg/kg body weight are all administered together 2 times daily for 1 week.
30-≤ 40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered 2 times daily for 1 week.
> 40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered 2 times daily for 1 week.

Renal and liver disease: Dose adjustment is not required in patients with impaired renal function/ Patients with severe liver disease should not require more than 20 mg Losec MUPS daily.

Patients with swallowing difficulties: The tablets may be dispersed in water or suspended in a small amount of fruit juice or yoghurt after gentle mixing. The dispersion should be taken immediately or within 30 minutes. It is important that the tablets should not be crushed or chewed.

4.3 Contraindications

Known hypersensitivity to omeprazole or to any of the other constituents of the formulation. Omeprazole like other PPIs should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

When gastric ulcer is suspected the possibility of malignancy should be excluded before treatment with Losec MUPS is instituted, as treatment may alleviate symptoms and delay diagnosis.

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

Some children with chronic illnesses may require long-term treatment although it is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the decreased intragastric acidity, the absorption of ketoconazole and itraconazole may be decreased during omeprazole treatment as it is during treatment with other acid secretion inhibitors or antacids.

Omeprazole undergoes oxidative metabolism which involves the cytochrome P450 enzyme system, and can prolong the elimination of diazepam, phenytoin, warfarin and other vitamin K antagonists which are in part substrates for this enzyme. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. However concomitant treatment with Losec MUPS 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with Losec MUPS 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. This is considered to be useful interaction during *H.pylori* eradication. There is no interaction with metronidazole or amoxicillin. These antimicrobials are used together with omeprazole for eradication of *Helicobacter pylori*.

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, ciclosporin, lidocaine, quinidine, estradiol, erythromycin, budesonide or antacids.

The absorption of Losec is not affected by alcohol or food.

There is no evidence of an interaction with piroxicam, diclofenac or naproxen. This is considered useful when patients are required to continue these treatments.

Interaction with other drugs also metabolised via the cytochrome P450 system cannot be excluded.

Co-administration of omeprazole (40mg once daily) with atazanavir 300 mg/ritonavir 100mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including omeprazole should not be co-administered with atazanavir (see section 4.3)

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus. Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. However, a dose adjustment of omeprazole is not required.

4.6 Pregnancy and lactation

Pregnancy

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus / newborn child indicating that, Losec can be used, if necessary during pregnancy.

Lactation

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

4.7 Effects on ability to drive and use machines

No effects are foreseen.

4.8 Undesirable effects

Losec MUPS is well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use, but in many cases a relationship to treatment with omeprazole has not been established.

The following definitions of frequencies are used:

Common $\geq 1/100$

Uncommon $\geq 1/1,000$ and $< 1/100$

Rare $< 1/1,000$

Common	<i>Central and peripheral nervous system</i> <i>Gastrointestinal</i>	Headache Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
Uncommon	<i>Central and peripheral nervous system</i> <i>Hepatic</i> <i>Skin</i> <i>Other</i>	Dizziness, paraesthesia, somnolence, insomnia and vertigo Increased liver enzymes Rash, dermatitis and/or pruritus, urticaria Malaise
Rare	<i>Central and peripheral nervous system</i> <i>Endocrine</i> <i>Gastrointestinal</i> <i>Haematological</i> <i>Hepatic</i> <i>Musculoskeletal</i> <i>Skin</i> <i>Renal and urinary disorders</i> <i>Other</i>	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients Gynaecomastia Dry mouth, stomatitis and gastrointestinal candidiasis Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia Encephalopathy in patients with pre-existing severe liver disease, hepatitis with or without jaundice, hepatic failure Arthralgia, muscular weakness and myalgia Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia Renal dysfunction Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia

The adverse event profile seen with the Losec MUPS Tablet is similar to that seen with the Losec Capsule.

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.

4.9 Overdose

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560mg have been described and occasional reports have been received when single oral doses have reached up to 2400mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment has been needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD); proton pump inhibitors

ATC code: A02B C01

Omeprazole reduces gastric acid secretion through unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible control of gastric acid secretion with once daily dosing.

Oral dosing with 20mg Losec MUPS once daily provides for rapid and effective inhibition of gastric acid secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80% in 24 hour intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70%, 24 hours after dosing with Losec MUPS.

Helicobacter pylori (*Hp*) is associated with acid peptic disease including duodenal ulcer (DU) and gastric ulcer (GU) in which about 95% and 80% of patients respectively are infected with this bacterium. *Hp* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *Hp* and gastric carcinoma.

Omeprazole has been shown to have a bactericidal effect on *Hp in vitro*.

In recent clinical studies using omeprazole 40mg daily, amoxicillin 1500mg daily and metronidazole 1200mg daily for 14 days overall *Hp* eradication rates of 93% and 89% were achieved (96% in metronidazole sensitive isolates).

Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged antisecretory treatment.

In recent clinical data in patients with acute peptic ulcer omeprazole *Hp* eradication therapy improved patients' quality of life.

During long-term treatment an increased frequency of gastric glandular cysts have been reported. These changes are a physiological consequence of pronounced inhibition of acid secretion. The cysts are benign and appear to be reversible. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

Paediatric data

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 GERD 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.

Eradication of *Helicobacter pylori* in children:

A randomized, double blind clinical study (Héliot study) has concluded to the efficacy and an acceptable safety for omeprazole associated to two antibiotics (amoxicillin and clarithromycin) in the treatment of *Helicobacter pylori* infection in children of 4 years old and above with a gastritis: *Helicobacter pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

Site and mechanism of action:

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

All pharmacodynamic effects observed are explained by the effect of omeprazole on acid secretion.

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole and omeprazole magnesium are acid labile and are administered orally as enteric-coated granules in capsules or tablets. Bioequivalence between Losec Capsules and Losec MUPS Tablets based on omeprazole plasma concentration-time curve (AUC) has been demonstrated.

Absorption takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of Losec MUPS is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

Elimination and metabolism

The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at a given time.

Omeprazole is entirely metabolised, mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole, these metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

5.3 Preclinical safety data

Animal Toxicology:

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any individual drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Glyceryl monostearate

Hyprolose

Hypromellose

Magnesium stearate

Methylacrylic acid – ethyl acrylate co-polymer (1:1) dispersion 30 per cent

Sugar spheres

Paraffin

Macrogol

Polysorbate

Crospovidone

Sodium stearyl fumarate

Sodium hydroxide*

Talc

Triethyl citrate

Iron oxide (E172)

Titanium dioxide (E171).

*May be used as a pH adjuster

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister packs of 28 tablets in an overlabelled outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 Parallel Product Authorisation Holder

IMED Healthcare Ltd
New Road
Buncrana
Co Donegal

8 Parallel Product Authorisation Number

PPA1463/21/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st August 2009

10 DATE OF REVISION OF THE TEXT