IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/019/002
Case No: 2068529

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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

Losec MUPS Gastro-Resistant Tablets 40mg

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 **28/08/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Losec MUPS Gastro-Resistant Tablets 40mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 41.3mg omeprazole magnesium equivalent to 40mg 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 tablet

Product imported from the UK
Dark red-brown, oblong, biconvex, gastro-resistant, film-coated tablets engraved with  on one side and 40 mg 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 20mg 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 40mg once daily in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks.

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

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

Maintenance treatment:
For prevention of relapse in patients with duodenal ulcer the recommended dose is Losec MUPS 10mg, once daily, increasing to 20mg 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 20mg once daily, reducing to 10mg once daily, if possible.

The recommended dosage is 20mg 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 40mg 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 weeks treatment.

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

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

Triple therapy regimens:
Losec MUPS and the following antimicrobial combinations:

Clarithromycin 250mg and metronidazole 400mg both twice a day for one week.
or
Amoxicillin 1g and clarithromycin 500mg both twice a day for one week.

Dual therapy regimens:

Losec MUPS 20mg twice daily with oral amoxicillin 1g twice daily for two weeks. Alternatively, Losec MUPS 40mg once daily and clarithromycin 500mg 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 instructions 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 40mg on the evening before surgery followed by Losec MUPS 40mg 2-6 hours prior to surgery.

Zollinger-Ellison syndrome:
The usual initial dose is 60mg Losec MUPS with subsequent adjustment to achieve optimal response in the range of 20-120mg daily. Doses above 80mg 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 gastroesophagal 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 20mg 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 PPI's 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 continous 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 continous 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, Cmax and Cmin). 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	≥1/100
Uncommon	≥1/1000 and <1/100
Rare	<1/1000

Common	*Central and peripheral Nervous system:*	Headache
	Gastrointestinal:	Diarrhoea, constipation, abdominal pain, nausea vomiting and flatulence
Uncommon	*Central and peripheral Nervous system:*	Dizziness, paraesthesia, somnolence, insomnia, and vertigo.
	Hepatic:	Increased liver enzymes.
	Skin:	Rash, dermatitis and/or pruritus, uricaria.
	Other:	Malaise.
Rare	*Central and peripheral Nervous system:*	Reversible mental confusion, agitation, aggression, depression, hallucinations predominantly in severely ill patients.
	Endocrine	Gynaecomastia.
	Gastrointestinal	Dry mouth, stomatitis , gastrointestinal candidiasis.
	Haematological	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.
	Hepatic	Encephalopathy in patients with pre-existing severe liver disease, hepatitis with or without jaundice, hepatic failure.
	Musculoskeletal	Arthralgia, muscular weakness and myalgia.
	Skin	Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia.
	Renal and urinary disorders	Renal dysfunction.
	Other:	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 omeprezole 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.

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%.

5.2 Pharmacokinetic properties

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 1year, 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

Cellulose microcrystalline
Glyceryl monostearate
Hyprolose
Hypromellose
Magnesium stearate
Methylacrylic acid – ethyl acrylate co-polymer (1:1)
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 expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C
Store in the original container

6.5 Nature and contents of container

Press-through Aluminium-Polyamide-PVC/Aluminium foil calendarised blister packs. Overlabelled packs of 7 tablets.

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

McDowell Pharmaceuticals
4 Altona Road
Lisburn BT27 5QB
N. Ireland

8 Parallel Product Authorisation Number

PPA 1473/19/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009

10 DATE OF REVISION OF THE TEXT