IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0970/044/005
Case No: 2040586

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

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

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

Losec 40 mg Powder for Solution for Infusion.

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 **22/01/2009**.

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 40 mg Powder for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for solution for infusion contains omperazole 40 mg (as omeprazole sodium).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
A sterile, lyophilised, white powder, for reconstitution as an intravenous infusion, supplied in a 10 ml, Type I glass vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of oesophageal reflux disease including reflux oesophagitis.
Treatment of duodenal and benign gastric ulcers, including those complicating NSAID therapy.
Prophylaxis of acid aspiration.
Zollinger-Ellison Syndrome.

4.2 Posology and method of administration

Dosage

Adults only
Treatment in patients where oral medication is inappropriate, e.g. in severely ill patients:

Losec 40mg given as an intravenous infusion once daily is recommended.

As a matter of good clinical practice, patients requiring long-term maintenance treatment should be reviewed periodically by the physician

Prophylaxis of acid aspiration

Losec 40mg given as an intravenous infusion to be completed one hour before surgery.

The i.v. infusion produces an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90%.

Clinical experience in Zollinger-Ellison syndrome is limited *(see section 5.1, Pharmacodynamic properties)*.

Administration

Losec powder for solution for infusion is for intravenous administration ONLY and must NOT be given by any other route.

Losec powder for solution for infusion should only be dissolved in either 100ml normal saline for infusion or 100ml 5% dextrose for infusion. No other solutions for i.v.infusion should be used.

After reconstitution from a microbiological point of view, use immediately (i.e. within 3 hours) and any unused portion should be discarded.

The duration of administration should be 20-30 minutes.

Use in the Elderly:

Dosage adjustment is not necessary.

Use in Children:

There is limited experience of use in children.

Impaired renal function:

Dose adjustment is not required in patients with impaired renal function.

Impaired hepatic function:

As half-life is increased in patients with impaired hepatic function, the dose requires adjustment and a daily dose of 10mg - 20mg may be sufficient.

4.3 Contraindications

Known hypersensitivity to any of the constituents of the formulation.
Omeprazole like other PPI's should not be administered with atazanavir *(see section 4.5, Interaction with other medicinal products and other forms of interaction).*

4.4 Special warnings and precautions for use

When gastric ulcer is suspected the possibility of malignancy should be excluded before treatment with Losec 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 and Campylobacter.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole therapy 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 when Losec is added to treatment. However, concomitant treatment with Losec 20mg 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 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 a useful interaction during *H. pylori* eradication.

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.

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, Contraindications)*

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and a 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 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, urticaria.
Other: Malaise.

Rare
Central and peripheral
Nervous system: Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.
Endocrine: Gynaecomastia.
*Gastrointestina*l: Dry mouth, stomatitis and 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.
Musculoskeleteal: 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, bronch-spasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

Isolated cases of irreversible visual impairment have been reported in critically ill patients who have received Losec Intravenous Injection, particularly at high doses, however no causal relationship has been established.

4.9 Overdose

Intravenous doses of up to 270mg on a single day and up to 650mg over a three-day period have been given in clinical trials without any dose related adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: AO2B CO1
Omeprazole reduces gastric acid secretion through a 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.

Intravenous administration of omeprazole results in an immediate reduction of intragastric acidity and a mean decrease over 24 hours of approximately 90% in patients with duodenal ulcer disease. A single 40mg i.v. dose has similar effect on intragastric acidity over a 24 hour period as either a single 80mg oral dose or repeated oral dosing with 20mg once daily. A higher dose of 60mg i.v. twice daily has been used in a clinical study in patients with Zollinger-Ellison syndrome.

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.

5.2 Pharmacokinetic properties

Distribution
The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiency. In elderly and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. The plasma protein binding of omeprazole is about 95%.

Metabolism and excretion
The average half-life of the terminal phase of the plasma concentration-time curve following i.v. administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during treatment.

Omeprazole is completely metabolised by the cytochrome P450 system, mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an intravenously given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from biliary secretion.

Elimination of omeprazole is unchanged in patients with reduced renal function. The elimination half-life is increased in patients with impaired liver function, but omeprazole has not shown any accumulation with once daily oral dosing.

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

Sodium hydroxide (for pH adjustment)
Disodium edetate

6.2 Incompatibilities

No other drugs should be mixed with reconstituted Losec Infusion solution.

6.3 Shelf Life

Unopened pack: 2 years.
Reconstituted solution: Chemical and physical in use stability of the product has been shown for 12 hours when dissolved in normal saline and 3 hours in 5% dextrose when stored at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

Any unused portion should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
Keep container in outer carton, in order to protect from light.

6.5 Nature and contents of container

Pack of 5, clear, Type I glass 10ml vials each containing omeprazole sodium 42.6 mg with grey bromobutyl stopper, blue polypropylene cap and golden aluminium frame.

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

The entire contents of each vial should be dissolved in approximately 5 ml and then immediately diluted to 100 ml. Normal saline for infusion or 5% dextrose for infusion should be used. No other solutions for i.v. infusion should be used.
Use on one patient during one treatment only.

DO NOT USE if any particles are present in the reconstituted solution.

Preparation:

1. With a syringe draw approximately 5 ml of infusion solution from the infusion bottle or bag.

2. Add the infusion solution to the vial containing the freeze dried omeprazole, mix thoroughly making sure all omeprazole is dissolved.

3. Draw the omeprazole solution back into the syringe.

4. Transfer the solution into the infusion bottle or bag.

5. Repeat 1-4 to make sure all omeprazole is transferred from the vial into the infusion bottle or bag.

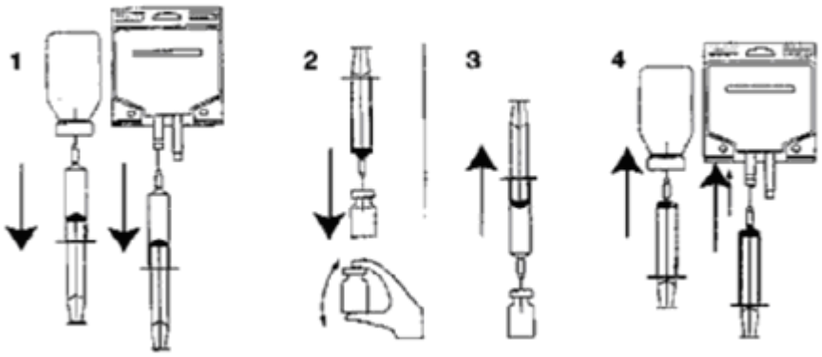
Alternative preparation for infusions in flexible containers:

(See attached diagrams)

1. Use a double ended transfer needle and attach to the injection membrane of the infusion bag. Connect the other needle-end from the vial with freeze-dried omeprazole.

2. Dissolve the omeprazole substance by pumping the infusion solution back and forth between the infusion bag and the vial.

3. Make sure all omeprazole is dissolved.



7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd
600 Capability Green
Luton
LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0970/044/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1992

Date of last renewal: 14 August 2007

10 DATE OF REVISION OF THE TEXT

January 2009