IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1485/001/003
Case No: 2072393

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

mibe GmbH Arzneimittel

Münchener Strasse 15, **Brehna**, **06796**, **Germany**

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

Soothome, 40 Milligram

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 **26/11/2009** until **31/05/2012**.

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

Soothome 40 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg of Omeprazole
Also contains sucrose
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Capsules, hard, with gastro-resistant granules.
Size 0 capsules with opaque blue cap and opaque orange body, containing white to beige granules

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Duodenal ulcers
- Benign gastric ulcers
- Reflux oesophagitis
- Maintenance treatment of reflux oesophagitis to prevent relapse
- Zollinger-Ellison syndrome
- Treatment of NSAID (Non Steroid Anti Inflammatory Drug) related gastric and duodenal ulcers
- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
- Symptomatic treatment of gastrooesophageal reflux disease
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated peptic ulcers (see 4.2 Posology and method of administration)

4.2 Posology and method of administration

Duodenal ulcers
The usual dose is 20 mg once daily. The duration of the treatment is 2-4 weeks.

Maintenance treatment: for prevention of recurrence a once daily 10 mg capsule is advised.

Benign gastric ulcers:
The usual dose is 20 mg once daily. The duration of the treatment is 4-(6)-8 weeks.

Reflux oesophagitis:
The usual dose is 20 mg once daily. The duration of treatment is 4-8 weeks.

Notes:
In isolated cases of duodenal ulcers, benign gastric ulcers and reflux oesophagitis the dosage of omeprazole can be increased to 40 mg omeprazole once daily.

Only if eradication therapy is not indicated or has been unsuccessful, duodenal and gastric ulcers may be treated with omeprazole monotherapy.

Children above 2 years and adolescents with severe reflux oesophagitis:
The clinical experience in children is limited. Omeprazole should only be used in children with severe reflux oesophagitis resistant to other therapeutic measures.
Treatment should be initiated by a hospital based paediatrician.
Continuous pH measurement and genotyping (concerning CYP 2C19 status) may be performed if appropriate for optimal therapeutic response.
The following dosage (equivalent to about 1 mg/kg/day) should be used:
Weight 10 kg to 20 kg: 10 mg/day
Weight over 20 kg: 20 mg/day

Treatment duration is usually 4 to 8 weeks and should not exceed 12 weeks due to lack of data with long-term use in this age group.

Maintenance treatment of reflux oesophagitis to prevent relapse:
The usual dose is 10 to 20 mg depending on the clinical response.

Zollinger-Ellison syndrome:
The dosage should be adjusted individually and continued under specialist supervision as long as clinically indicated. The recommended initial dosage is 60 mg once daily. With doses above 80 mg daily, the dose should be divided and given twice daily. In patients with Zollinger-Ellison syndrome the treatment is not subject to a time limit.

Treatment of NSAID related gastric and duodenal ulcers:
The usual dose is 20 mg daily. The treatment duration is 4 to 8 weeks.

Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse:
The usual dose is 20 mg daily.

Symptomatic treatment of gastroesophageal reflux disease:
The usual dose is 10 to 20 mg daily depending on clinical response. The treatment duration is 2 to 4 weeks.
If the patient does not experience any improvement in symptoms after a 2 week treatment further examinations should be performed.

Eradication therapy:
Patients with peptic ulcers due to *Helicobacter pylori* infection should be treated with eradication therapy with appropriate combinations of antibiotics with adequate dosing regimens. The selection of an appropriate regimen should be based on patient tolerability and therapeutic guidelines. The following combinations have been tested:

- Omeprazole 20 mg, Amoxicillin 1000 mg, Clarithromycin 500 mg all 2 times daily
- Omeprazole 20 mg, Clarithromycin 250 mg, Metronidazole 400-500 mg all 2 times daily

The treatment duration for the eradication is 1 week. To avoid the development of resistance the treatment duration should not be reduced.
In patients with active ulcers an extension of the therapy with omeprazole-monotherapy according to the posology and treatment duration given above may be performed.

Combination therapy including metronidazole should not be considered as first choice because of the carcinogenic potential of metronidazole. The application of metronidazole should be restricted to treatment periods of less than 10 days.

Elderly:
Dose adjustment is not required in the elderly.

Children:
Omeprazole should not be used in children under 2 years of age.

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

Impaired hepatic function:
As bioavailability and half-life can increase in patients with impaired hepatic function, the dose requires adjustment with a maximum daily dose of 20 mg.

Method of administration:
The capsules should be swallowed whole with sufficient fluid (e.g. 1 glass of water) before a meal (e.g. before breakfast or dinner) or on an empty stomach. The capsules should not be chewed or milled.

In patients with swallowing difficulties, the capsules may be opened and the contents swallowed alone or suspended in a small amount fruit juice or yoghurt after gentle mixing. The resulting dispersion should be taken immediately.

4.3 Contraindications

Omeprazole is contraindicated in patients with hypersensitivity to omeprazole or to any of the excipients.

Combination therapy with clarithromycin should not be used in patients with hepatic impairment.

Omeprazole should not be administered with atazanavir due to an important reduction in atazanavir exposure (see section 4.5)

4.4 Special warnings and precautions for use

In patients with peptic ulcer disease *Helicobacter pylori*-status should be determined if relevant. In patients who are shown to be *Helicobacter pylori*-positive, the elimination of the bacterium by eradication therapy should be aimed wherever possible.

If a gastric ulcer is suspected, the possibility of malignancy must be excluded before treatment with Omeprazole capsules is instituted, as treatment may alleviate symptoms and delay diagnosis.

The diagnosis of reflux oesophagitis should be confirmed endoscopically.

Decreased gastric acidity, due to any means - including proton-pump inhibitors – increases gastric counts of bacteria normally present in the gastro-intestinal tract. Treatment with acid-reducing medicinal products leads to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

In patients with severe impaired hepatic function, liver enzyme values should be checked periodically during treatment with Omeprazole capsules.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

To ensure better efficacy in treatment of NSAID-related ulcers, the possibility of stopping the intake of the causative agent should be strongly considered.

The maintenance treatment of ulcers associated with the intake of NSAIDs should be restricted to patients at risk.

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and thorough risk-benefit assessment should be performed in long-term use exceeding 1 year.

During therapy with omeprazole requiring a combined administration of medicinal products (NSAID related ulcers or eradication) caution should be exercised when administering additional medicinal products as interactions might add up or potentiate (see section 4.5 Interaction with other medicinal products and other forms of interaction).

During combination treatment caution should also be exercised in patients with renal or hepatic dysfunction (for dose restriction see 4.2 Posology and method of administration).

Omeprazole should not be used in infants and children under the age of 2 years (see section 4.2).

Although not known for orally administered omeprazole, blindness and deafness have been reported in the use of the injection form of omeprazole; therefore, in severely ill patients the monitoring of visual and auditory senses is recommended.

This medicinal product contains 1.306 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

As omeprazole is metabolised in the liver through cytochrome P450 isoforms (mainly CYP 2C19, S-mephenytoin hydroxylase) and inhibits enzymes of the CYP2C subfamily (CYP 2C19 and CYP 2C9) it can delay the elimination of other active substances metabolised by these enzymes. This has been observed for diazepam (and also of other benzodiazepines such as triazolam or flurazepam), phenytoin and warfarin. Periodic monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be necessary . Other active substances that could be affected are hexabarbital, citalopram, imipramine, clomipramine etc. Omeprazole may inhibit the hepatic metabolism of disulfiram. Some possibly related cases of muscular rigidity have been reported.

There are contradictory data on the interaction of omeprazole with ciclosporin and tacrolimus. Therefore, the plasma levels of ciclosporin and tacrolimus should be monitored in those patients treated with omeprazole, because an increase in ciclosporin levels is possible.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration.

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

Simultaneous treatment with omeprazole and digoxin in healthy subjects lead to a 10% increase in the bioavailability of digoxin as a consequence of the increased gastric pH.

Omeprazole may reduce the oral absorption of vitamin B12. This should be taken into account in those patients with low basal levels who undergo a long-term treatment with omeprazole.

Because of potential clinically significant interaction St. John's wort should not be used concomitantly with omeprazole.

Co-administration of omeprazole 40 mg O.D. with atazanavir 300 mg/ritonavir 100 mg O.D. 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. Thus proton pump inhibitors should not be co-administered with atazanavir.
Although not studied, other daily doses of omeprazole may produce similar results and, therefore, also co-administration of any other doses of omeprazole is contraindicated (see section 4.3).

Concomitant administration of omeprazole and the combined inhibitor of CYP2C19 and CYP3A4, voriconazole, increased esomeprazole AUC by 280%. A dose adjustment of esomeprazole is not regularly required. However, dose adjustment should be considered in patients with severe hepatic impairment, those receiving a high dose, and if long-term treatment is indicated.

There is no evidence of an interaction of omeprazole with caffeine, propranolol, theophylline, metoprolol, lidocaine, quinidine, erythromycin, phenacetin, estradiol, amoxicillin, budesonide, diclofenac, metronidazole, naproxen, piroxicam, or antacids. The absorption of omeprazole is not affected by alcohol.

4.6 Pregnancy and lactation

Limited epidemiologic studies indicate no adverse effects on pregnancy or increases in general malformation rate. However, there is insufficient information with respect to specific abnormalities.

In rats, omeprazole and its metabolites are excreted into milk. There is insufficient data on exposure of babies via breast milk. Omeprazole concentration in human breast milk reaches approximately 6% of the maximum plasma concentration in the mother.

Use of omeprazole during pregnancy and lactation requires a careful benefit-risk assessment.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed. However, apart from side effects affecting the CNS or visual abilities (see 4.8.), no effects on the ability to drive are expected from the intake of omeprazole.

4.8 Undesirable effects

The following definitions apply to the incidence of the undesirable effects:

- very common (>1/10)
- common (>1/100, <1/10)
- uncommon (>1/1,000, <1/100)
- rare (>1/10,000, <1/1,000)
- very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and the lymphatic system disorders	Rare: Hypochrome, microcytic anaemia in children. Very rare: changes in blood count, reversible thrombocytopenia, leucopenia or pancytopenia and agranulocytosis.
Immunosystem disorders	Very rare: urticaria, elevated body temperature, angioedema, bronchoconstriction, or anaphylatic shock, allergic vasculitis and fever.
Nervous system disorders	Common: somnolence, sleep disturbances (insomnia), dizziness, headaches and drowsiness. These complaints usually improve during continued therapy. Rare: Paresthesia and light headedness. Mental confusion and hallucinations in predominantly severely ill or elderly patients. Very rare: agitation and depressive reactions in predominantly severely ill or elderly patients.
Eye disorders	Uncommon: visual disturbances (blurred vision, loss of visual acuity or reduced field of vision). These conditions usually resolve on cessation of therapy.
Ear and labyrinth disorders	Uncommon: auditory dysfunction (e.g. tinnitus). These conditions usually resolve on cessation of therapy.
Gastrointestinal disorders	Common:

	diarrhoea, constipation, flatulence (possibly with abdominal pain), nausea and vomiting. In the majority of these cases the symptoms improve if the therapy is continued. Uncommon: taste disturbances. This condition usually resolves on cessation of therapy. Rare: brownish-black discoloration of the tongue during concomitant administration of clarithromycin and benign glandular cysts: both were reversible after cessation of treatment. Very rare: dryness of the mouth, stomatitis, candidiasis or pancreatitis.
Hepato-biliary disorders	Uncommon: changes in liver enzyme values (which resolve after discontinuation of therapy). Very rare: hepatitis with or without jaundice, hepatic failure and encephalopathy in patients with pre-existing severe liver disease.
Skin and subcutaneous tissue disorders	Uncommon: pruritus, skin eruptions, alopecia, erythema multiforme or photosensitivity and increased tendency to sweat. Very rare: Stevens-Johnson-syndrome or toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Rare: muscle weakness, myalgia and joint pain.
Renal and urinary disorders	Very rare: nephritis (interstitial nephritis)
Other adverse effects:	Uncommon: general malaise, peripheral oedema (which resolved on cessation of therapy) Very rare: hyponatremia, gynaecomastia.

4.9 Overdose

There is no information available on the effects of overdosage of omeprazole in humans.
Large single oral doses up to 160 mg/day and daily doses up to 400 mg as well as intravenous single doses up to 80 mg and daily intravenous doses up to 200 mg or 520 mg in 3 days, respectively, have been tolerated without undesirable effects.

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, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. Omeprazole directly and dose-dependently inhibits the enzyme H^+, K^+-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound

receptors (such as the histamine H_2, muscarine M_1 or gastrinergic receptors), omeprazole has been assigned to a separate class of acid-inhibiting agents, which block the final step of acid production.

As a consequence of its mode of action, omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type.
Thus, omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

As a weak base the prodrug omeprazole accumulates in the acid environment of the parietal cells and will only become effective as an inhibitor of the H^+, K^+-ATPase after being protonised and rearranged.
In an acid environment at a pH of less than 4 the protonised omeprazole is converted to omeprazole sulphenamide, the active substance proper.

Compared to the plasma half-life of the omeprazole base, omeprazole sulphenamide remains in the cell for a longer period of time (see 5.2 Pharmacokinetic properties). A sufficiently low pH-value is only found in the gastric parietal cells; this explains the high specificity of omeprazole. It is the omeprazole sulphenamide that binds to the enzyme and inhibits its activity.

If the enzyme-system is inhibited, the pH-value increases and less omeprazole accumulates or is converted in the gastric parietal cells. Consequently, the accumulation of omeprazole is regulated by a kind of feedback-mechanism.

In long-term treatment, omeprazole, as a result of acid inhibition, causes a moderate gastrin increase. Mild to moderate increase in ECL-cells occurs during long-term use. Carcinoids as found in animal experiments (see 5.3 Preclinical safety data) were not seen in humans yet.

Most available clinical experience form controlled randomised clinical trials indicate that omeprazole 20 mg twice daily in combination with two antibiotics for 1 week achieve >80% *Helicobacter pylori* eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *Helicobacter pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *Helicobacter pylori* eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antibacterial agent should be taken into account in the considerations for a new re-treatment regimen.

Clinical evidence additionally indicates that, following successful eradication therapy in patients with peptic ulcer disease, relapse rates, duodenal ulcers and most likely also gastric ulcers are exceptionally low in comparison to the natural course of the disease with ongoing infection.

5.2 Pharmacokinetic properties

Omeprazole is acid labile and is administered orally as gastro-resistant granules in hard-gelatin capsules. Absorption takes place in the small intestine.

Peak plasma concentrations of omeprazole occur within 1 to 3 hours after administration. The plasma half-life is about 40 minutes, and the total plasma clearance is 0.3 to 0.6 l/min. In a small percentage of the patients (CYP 2 C19 poor metabolisers) a reduced elimination rate of omeprazole has been observed.

In these cases, the terminal elimination half-life can be approximately 3 times as long as the normal value, and the area under the plasma concentration-time curve (AUC) can increase by up to 10 times.

The distribution volume of omeprazole in the body is relatively small (0.3 l/kg of body weight) and corresponds to that of the extracellular fluid. Approximately 95% is protein bound.

Omeprazole accumulates as a weak base in the acid environment of the intracellular channel system of the parietal cells. In this acid environment omeprazole is protonised and converted into the active substance, omeprazole sulphenamide. The active substance binds covalently to the gastric proton pump (H^+, K^+-ATPase) on the secretory

surface of the gastric parietal cell and inhibits its activity. The duration of the inhibition of acid secretion is therefore substantially longer than the period in which omeprazole-base is present in plasma. The degree of inhibition of acid secretion is directly correlated to the area under the plasma concentration-time curve (AUC) but not to the plasma concentration at any given time.

Omeprazole is entirely metabolised, mainly in the liver by CYP 2C19. A small percentage of the patients lack a functional CYP2C19 enzyme and have reduced elimination rate of omeprazole. The sulphone, sulphide and hydroxy-omeprazole are found in plasma. These metabolites have no significant effect on acid secretion.
About 20% of administered dose is excreted in faeces and the remaining 80% is excreted in urine as metabolites. The two major urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

In patients with renal impairment the kinetics of omeprazole was very similar to that in healthy subjects. But, because the renal elimination is the most important excretory pathway for metabolised omeprazole, the elimination rate is reduced to a degree corresponding to the reduction in renal function. If omeprazole is given once daily, accumulation can be avoided.

The bioavailability of omeprazole is slightly elevated in the elderly, and the elimination rate is slightly diminished. But the individual values are nearly equal to that of young healthy subjects, and there is no indication that the tolerance in elderly patients treated with normal doses of omeprazole is reduced.

After intravenous administration of 40 mg omeprazole for 5 days, the absolute measured bioavailability increased by about 50%; this can be explained by decreased hepatic clearance due to saturation of the CYP2C19 enzyme.

In patients with chronic hepatic disease the clearance of omeprazole is reduced, and the plasma half-life can increase up to approximately 3 hours. The bioavailability can then be greater than 90%. Omeprazole given in a dosage regime of 20 mg once daily for 4 weeks was tolerated well, and no accumulation of omeprazole or its metabolites was observed.
The bioavailability of a single oral dose of omeprazole is approximately 35%. With repeated administration the bioavailability increases to approximately 60%. In patients with restricted hepatic function it can increase to over 90% due to a reduced first pass effect.

Simultaneous intake with food lower the absorption rate.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for human based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres
Sodium starch glycollate Type A
Sodium laurilsulfate
Povidone K30
Potassium oleate
Hypromellose
Methacrylic acid-ethyl acrylate copolymer
Triethyl citrate
Titanium dioxide (E171)
Talc
Erythrosine (E127)
Quinoline yellow (E104)

Indigo carmine (E132)
Gelatin

Printing Ink
Shellac
Ethyl Alcohol anhydrous
Isopropyl alcohol
Propylene glycol
N-Butyl Alcohol
Polyvinylpyrrolidone
Sodium hydroxide
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC. Keep the bottle tightly closed. Store in the original package.

6.5 Nature and contents of container

HDPE bottle and polypropylene cap with integral silica gel dessicant
Pack sizes: 5, 7, 14, 15, 20, 21, 28, 30, 42, 50, 56, 60, 84, 98, 100 or 500 Capsules

Not all pack sizes may be marketed

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 MARKETING AUTHORISATION HOLDER

mibe GmbH Arzneimittel
Münchener Strasse 15
Brehna
06796
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1485/1/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st June 2007.

10 DATE OF REVISION OF THE TEXT

April 2008