IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0593/035/001
Case No: 2035433

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

Stada Arzneimittel AG

Stadastrasse 2-18, **D-61118 Bad Vilbel**, **Germany**

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

Omeprazole 20 Milligram Tablets Gastro-Resistant

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 **09/08/2007** until **25/06/2010**.

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

Omeprazole 20 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gastro-resistant tablet contains 20.0 mg omeprazole.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

Round, light grey coated tablets

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 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 H. pylori in patients with H. pylori associated peptic ulcers (see section 4.2.)

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.

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 the 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.

Monotherapy with omeprazole alone in duodenal and gastric ulcers should only be used in patients in whom eradication therapy is not indicated.

Children above 2 years 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 should be used:
Weight 10 kg to 20 kg: 10 mg/day
Weight over 20 kg: 20 mg/day.
(approx. 1 mg/kg/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 gastro-duodenal ulcers due to H. pylori infection should be treated with eradication therapy with appropriate combinations of antibiotics with adequate dosing regimens.
The selection of 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 its carcinogenic potential. The application of metronidazole should be restricted to treatment periods of less than 10 days.

Elderly:
Dose adjustment is not required in the elderly.

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.

The gastro-resistant tablets should be swallowed whole with sufficient fluid (e.g. 1 glass of water) strictly before a meal (e.g. before breakfast or dinner) or on empty stomach.

4.3 Contraindications

Omeprazole is contraindicated in patients with known hypersensitivity to omeprazole or any other component of the formulation.
Combination therapy with clarithromycin should not be used in patients with hepatic impairment.

4.4 Special warnings and precautions for use

In patients with peptic ulcer disease Helicobacter pylori-status should be determined if relevant. At patients who are shown to be Helicobacter pylori-positive, the elimination of the germ 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 Stada 20 mg 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 drugs leads to a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter.

Omeprazole should be used with caution in elderly and in hepatic and renal dysfunction, especially in high doses.

In patients with severe impaired hepatic function, liver enzyme values should be checked periodically during treatment with Omeprazole Stada 20 mg.

This medicine contains lactose. Patients with rare hereditary problems of lactase insufficiency, galactosaemia or glucose/galactose malabsorption should not take this medicine.

Before the treatment of NSAID-related ulcers, the possibility of stopping the intake of the causative agent should strongly be considered.

The maintenance treatment of ulcers associated with the intake of non-steroidal anti-inflammatory drugs should be restricted to patients at risk.

In long-term use especially when exceeding 1 year, a regular review of the treatment and a periodic and thorough benefit-risk assessment should be performed by the physician.

During therapy with omeprazole requiring a combined administration of drugs (NSAID related ulcers or eradication) caution should be exercised when administering additional drugs as interactions might add up or potentiate (see SPCs of the drugs).

During combination treatment caution should also be exercised in patients with renal or hepatic dysfunction (for dose restriction see section 4.2.).

Omeprazole should not be used in infants and children under the age of 2.

In severely ill patients the monitoring of visual and auditory senses is recommended as isolated cases of blindness and deafness have been reported in the use of the injection form of omeprazole.

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 drugs metabolised by these enzymes.
This has been observed for diazepam (and also of other benzodiazepines 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 drugs that could be affected are hexabarbital, citalopram, imipramine, clomipramine etc.

Omeprazole may inhibit the hepatic metabolism of disulfiram. Some possibly related isolated cases of muscular rigidity have been reported.

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

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

Coadministration of atazanavir, ritonavir and omeprazole is expected to decrease atazanavir plasma concentrations (diminished therapeutic effect) and is therefore not recommended.

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.

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

Tabular overview of the important interactions of Omeprazole Stada 20 mg:

Other drug	Reason	Resulting effect
Diazepam (and probably other benzodiazepines) R-Warfarin Phenytoin	Interaction with the Cytochrome 450 CYP 2C metabolising enzyme	Delayed elimination and elevated plasma levels
Ketoconazole Itraconazole (and others with pH-dependant absorption)	Elevation of the gastric pH	Reduced absorption
Digoxin	Elevation of the gastric pH	10% increase in bioavailability
Clarithromycin Roxithromycin Erythromycin (presumably other macrolides as well)	Gastric pH change and altered metabolism in the liver	Elevated plasma concentrations, increased bioavailability and prolonged half-life of omeprazole
St. John's wort	Induction of Cytochrome P450 2C19-mediated omeprazole metabolism	Reduced serum concentration of omeprazole
Atazanavir/ Ritonavir	exact mechanism currently unknown	Decreased plasma concentrations of atazanavir (diminished therapeutic effect)
Alcohol Amoxicillin Budesonide Quinidine Caffeine Diclofenac Estradiol Lidocaine Metoprolol Metronidazole Naproxen Phenacetin Piroxicam Propranolol S-Warfarin Theophylline		No alteration of the pharmacokinetics

4.6 Pregnancy and lactation

Limited epidemiologic studies indicate no adverse effects of omeprazole 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 ca 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 with concomitant intake of omeprazole have been performed. However, apart from undesirable effects affecting the CNS or visual abilities (see chapter 4.8), no effects on the ability to drive are expected from the intake of omeprazole.

4.8 Undesirable effects

Gastrointestinal disorders
Common (10-1%): diarrhoea, constipation, flatulence (possibly with abdominal pain), nausea and vomiting. In the majority of these cases the symptoms improve if the therapy is continued.
Rare (0.1%-0.01%): brownish-black discoloration of the tongue during concomitant administration of clarithromycin and benign glandular cysts; both were reversible after cessation of treatment
Very rare (<0.01%): dryness of the mouth, stomatitis, candidiasis or pancreatitis

Hepato-biliary disorders
Uncommon (1%-0.1%): changes in liver enzyme values (which resolve after discontinuation of therapy)
Very rare (<0.01%): hepatitis with or without jaundice, hepatic failure and encephalopathy in patients with pre-existing severe liver disease

Blood and the lymphatic system disorders
Very rare (<0.01%): changes in blood count, reversible thrombocytopenia, leucopenia or pancytopenia and agranulocytosis
Rare (0.1%-0.01%): Hypochromia, microcytic anaemia in children

Skin and subcutaneous tissue disorders
Uncommon (1%-0.1%): pruritus, skin eruptions, alopecia, erythema multiforme or photosensitivity and increased tendency to sweat
Very rare (<0.01%): Stevens-Johnson syndrome or toxic epidermal necrolysis

Musculoskeletal disorders
Rare (0.1%-0.01%): muscle weakness, myalgia and joint pain.

Renal disorders
Very rare (<0.01%): nephritis (interstitial nephritis)

Nervous system disorders
Common (1%-10%): drowsiness, somnolence, sleep disturbances (insomnia), vertigo and headaches. These complaints usually improve during continued therapy.
Rare (0.1%-0.01%): Paresthesia and light headedness. Mental confusion and hallucinations in predominantly severely ill or elderly patients.
Very rare (<0.01%): agitation and depressive reactions in predominantly severely ill or elderly patients.

Disorders in sensory organs
Uncommon (1%-0.1%): visual disturbances (blurred vision, loss of visual acuity or reduced field of vision) and auditory dysfunction (e. g. tinnitus) or taste disturbances. These conditions usually resolve on cessation of therapy.

Hypersensitivity reactions
Very rare (<0.01%): urticaria, elevated body temperature, angioedema, bronchoconstriction, or anaphylactic shock, allergic vasculitis and fever have been reported.

Other adverse effects
Uncommon (1%-0.1%): peripheral oedema (which resolved on cessation of therapy)
Very rare (<0.01%): hyponatremia, gynaecomastia

4.9 Overdose

Symptoms
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 adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective proton pump inhibitor, substituted benzimidazole

ATC -Code: A02B C 01

Omeprazole 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 that is independent of 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 Section 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) were not seen in humans yet.

Most available clinical experience from controlled randomised clinical trials indicate that omeprazole 20 mg twice daily in combination with two antibiotics for 1 week achieve >80% H. pylori eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant H. 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 H. 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 retreatment regimen.
Clinical evidence additionally indicates that, following successful eradication therapy in patients with peptic ulcer disease, relapse rates of 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

General pharmacokinetics

Omeprazole is acid labile and is administered orally as gastro-resistant tablets. 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 2C19 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 covalent 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 CYP 2C19 enzyme and have a 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 CYP 2C19 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.

For Omeprazole Stada 20 mg gastro-resistant tablets bioequivalence with the originator product has been demonstrated in single dose and repeated dose studies.

The effect of a high fat meal on the bioavailability of Omeprazole Stada 20 mg gastro-resistant tablets has been tested in multiple and single dose studies. The absorption of omeprazole from both test and reference preparation is delayed and reduced under the influence of a high fat meal.
Therefore Omeprazole Stada 20 mg gastro-resistant tablets should strictly be taken before meals or on empty stomach.

5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans.
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.
In mutagenicity studies (in-vitro and in-vivo) no findings of clinical relevance did occur.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex
Lactose monohydrate
Maize starch
Sodium starch glycollate (type A)
Magnesium stearate
Hypromellose phthalate
Acetylated monoglyceride
Titanium dioxide (E 171)
Ferric oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life is 2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister: polyamide/aluminium/PVC-aluminium
7, 10, 14, 15, 28, 30, 50, 56, 60, 100 and 500 gastro-resistant tablets

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

Stada Arzneimittel AG
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Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/35/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th October 2002
Date of last renewal: 26th June 2005

10 DATE OF REVISION OF THE TEXT

October 2005