Public Assessment Report

Decentralised Procedure

Esomeprazole 20 mg gastro-resistant tablets
Esomeprazole 40 mg gastro-resistant tablets

UK/H/2916 & 4424-5/001-2/DC
UK licence numbers: PL 15773/0778-9 & 0901-4

Ratiopharm GmbH
LAY SUMMARY

On 24th August 2011, the MHRA granted Ratiopharm GmbH Marketing Authorisations (licences) for the medicinal products Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0778-9, 0901-2 and 0903-4). These are prescription-only medicines (POM).

The active ingredient, esomeprazole, belongs to a group of medicines called ‘proton pump inhibitors’, which work by reducing the amount of acid that your stomach produces. Esomeprazole 20 mg and 40 mg gastro-resistant tablets are used to treat the following:

In adults and young people aged 12 years and above:

- ‘Gastro-oesophageal reflux disease’ (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called ‘Helicobacter pylori’. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

In adults:

- Stomach ulcers caused by medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Esomeprazole gastro-resistant tablets can also be used to stop stomach ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
- Prolonged treatment after prevention of rebleeding of ulcers with intravenous esomeprazole.

Esomeprazole 20 mg and 40 mg gastro-resistant tablets were considered to be generic versions of the UK reference products Nexium® 20 mg and 40 mg tablets (PL 17901/0068 and 0069, AstraZeneca AB) based on the data submitted by Ratiopharm GmbH.

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Esomeprazole 20 mg and 40 mg gastro-resistant tablets outweigh the risk; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Initial Procedure

| Product Name                  | Esomeprazole 20 mg gastro-resistant tablets  
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<td>Esomeprazole 40 mg gastro-resistant tablets</td>
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| MA Holder                    | Ratiopharm GmbH,
|                              | Graf-Arco-Strasse 3, D-89079 Ulm            |
| Reference Member State (RMS)| UK                                          |
| Concerned Member States (CMS)| UK/H/2916/001-2/DC: Austria, Bulgaria, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain and Sweden |
|                              | UK/H/4424/001-2/DC: Germany                  |
|                              | UK/H/4425/001-2/DC: Germany                  |
| Procedure Numbers            | UK/H/2916 & 4424-5/001-2/DC                 |
| Timetable                    | End of Procedure: Day 210 – 6th July 2011   |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0778-9, 0901-2 and 0903-4) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Esomeprazole 20 mg gastro-resistant tablets
Esomeprazole 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Esomeprazole 20/40 mg gastro-resistant tablets:
Each gastro-resistant tablet contains 20/40 mg esomeprazole (as esomeprazole magnesium).

Excipients: lactose, sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Esomeprazole 20 mg gastro-resistant tablets:
Brick red coloured, round shape, biconvex, film-coated tablet, imprinted with “20” on one side.

Esomeprazole 40 mg gastro-resistant tablets:
Brick red coloured, round shape, bevelled edge, biconvex, film-coated tablet imprinted with “40” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Esomeprazole tablets are indicated for:

Gastro-oesophageal Reflux Disease (GORD)
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and
- healing of Helicobacter pylori associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers

Patients requiring continued NSAID therapy
- healing of gastric ulcers associated with NSAID therapy
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk

Treatment of Zollinger Ellison Syndrome

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers

4.2 Posology and method of administration

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

For patients who have difficulty in swallowing the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.
For patients who cannot swallow, the tablets can be administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested. For preparation and administration instructions see section 6.6.

**Posology**

**Adults and adolescents from the age of 12 years**

**Gastro-oesophageal Reflux Disease (GORD)**
- treatment of erosive reflux oesophagitis
  40 mg once daily for 4 weeks.
  An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed oesophagitis to prevent relapse
  20 mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease (GORD)
  20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

**In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and**
- healing of Helicobacter pylori associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.
  20 mg esomeprazole with for example 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

When selecting appropriate combination therapy, consideration should be given to official national, regional and 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.

**Adults**

**Patients requiring continued NSAID therapy**
- Healing of gastric ulcers associated with NSAID therapy:
  The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

- Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:
  20 mg once daily.

**Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.**
40 mg once daily for 4 weeks after i.v. induced prevention of rebleeding of peptic ulcers.

**Treatment of Zollinger Ellison Syndrome**
The recommended initial dosage is esomeprazole 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

**Impaired renal function**
Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

**Impaired hepatic function**
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg esomeprazole should not be exceeded (see section 5.2).
Elderly
Dose adjustment is not required in the elderly.

Paediatric patients
Gastro-oesophageal Reflux Disease (GORD)
- Treatment of endoscopically proven erosive reflux oesophagitis
  Weight ≥ 20 kg: 10 mg or 20 mg once daily for 8 weeks. (Other esomeprazole products are available for the treatment at a dose of 10 mg.)

Esomeprazole 20 mg gastro-resistant tablets are not indicated for the use in children less than 20 kg body weight.

Esomeprazole 40 mg gastro-resistant tablets are not indicated for the use in children younger than 12 years.

The experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended (see section 5.1).

4.3 Contraindications
Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole should not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see section 4.5).

When prescribing esomeprazole for eradication of Helicobacter pylori possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter (see section 5.1).

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.
4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other drugs

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75 % decrease in AUC, $C_{\text{max}}$ and $C_{\text{min}}$). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30 % in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, $C_{\text{max}}$ and $C_{\text{min}}$ by 36–39 % and mean AUC, $C_{\text{max}}$ and $C_{\text{min}}$ for the pharmacologically active metabolite M8 was reduced by 75-92 %. For saquinavir (with concomitant ritonavir), increased serum levels (80-100 %) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir). Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Drugs metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. Concomitant administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) $C_{\text{max}}$ and AUC by 15 % and 41 %, respectively.

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QT$_C$ interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin, quinidine, quindine.

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.
In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46 % (Day 1) and 42 % (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47 % (24 hours) and 30 % (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

Effects of other drugs on the pharmacokinetics of esomeprazole
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280 %. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are limited amount of data from the use of esomeprazole in pregnant women. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor fetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development (see section 5.3). Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of esomeprazole during pregnancy.

Lactation
It is unknown whether esomeprazole is excreted in human breast milk. A risk to the suckling child cannot be excluded. Therefore esomeprazole should not be used during breast-feeding.

Fertility
There are no data on the effects of esomeprazole on human fertility. Fertility was unaffected following omeprazole treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines
No effects have been observed.

4.8 Undesirable effects
The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (common ≥ 1/100, to < 1/10; uncommon ≥ 1/1,000, to < 1/100; rare ≥ 1/10,000, to < 1/1,000; very rare < 1/10,000).

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia

Immune system disorders
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: Peripheral oedema
Rare: Hyponatraemia
Very rare: Hypomagnesaemia

Psychiatric disorders
Uncommon: Insomnia
RARE: Agitation, confusion, depression
VERY RARE: Aggression, hallucinations

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders
Rare: Blurred vision

Ear and labyrinth disorders
Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Rare: Malaise, increased sweating

4.9 Overdose
There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: proton pump inhibitor
ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
**Site and mechanism of action**

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme \( \text{H}^+\text{K}^-\text{ATPase} \) – the acid pump and inhibits both basal and stimulated acid secretion.

**Effect on gastric acid secretion**

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90 % when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76 %, 54 % and 24 %. Corresponding proportions for esomeprazole 40 mg were 97 %, 92 % and 56 %.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

**Therapeutic effects of acid inhibition**

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78 % of patients after four weeks, and in 93 % after eight weeks.

One week treatment with esomeprazole 20 mg twice daily and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90 % of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIA or IIB (9 %, 43 %, 38 % and 10 % respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9 % in the esomeprazole treated group compared to 10.3 % for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group 7.7 % vs. 13.6 %.

**Other effects related to acid inhibition**

During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged > 60 and/or with previous ulcer), including COX-2 selective NSAIDs.
Paediatric patients
In a placebo-controlled study (98 patients aged 1-11 months) efficacy and safety in patients with signs and symptoms of GORD were evaluated. Esomeprazole 1 mg/kg once daily was given for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening.

In a placebo-controlled study (52 patients aged < 1 month) efficacy and safety in patients with symptoms of GORD were evaluated. Esomeprazole 0.5 mg/kg once daily was given for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GORD.

Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg esomeprazole in < 1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-oesophageal pH< 4.

The safety profile appeared to be similar to that seen in adults.

5.2 Pharmacokinetic properties
Absorption and distribution
Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64 % after a single dose of 40 mg and increases to 89 % after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50 % and 68 % respectively. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97 % plasma protein bound.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80 % of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1 % of the parent drug is found in urine.

Special patient populations
Approximately 2.9±1.5 % of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100 % higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %.
These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

**Impaired organ function**
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

**Paediatric**
*Children 1–11 years:*
Following repeated dose administration of 10 mg esomeprazole, the total exposure (AUC) was similar within the age range 1 to 11 years and the exposure was similar to the exposure seen with the 20 mg dose in adolescents and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to the same dose in adolescents and adults.

*Adolescents 12-18 years:*
Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data
Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 9 times the maximum human omeprazole dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals. Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- cellulose, microcrystalline
- talc
- lactose monohydrate
- maize starch
- macrogol 8.000
- methacrylic acid - ethyl acrylate copolymer (1:1)
- sodium laurilsulfate
- polysorbate 80
- copovidone
- crospovidone type A
- sugar spheres (sucrose and maize starch)
- povidone
- hypromellose
- light magnesium oxide
- magnesium stearate
diethyl phthalate
silica, colloidal anhydrous
titanium dioxide (E171)
ethylcellulose
iron oxide red (E172)
Opacode S-1-17823 black ink containing iron oxide black (E172), shellac, propylene glycol and ammonium hydroxide.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blisters and HDPE bottle:
2 years

HDPE bottle:
Shelf life after first opening: 100 days

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container
For PLs 15773/0778-9
Aluminium/aluminium blister packs.
Pack size: 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 100x1

HDPE bottles with white PP closures with induction sealing wad and desiccant (silica gel canister).
Bottle size: 100, 150

For PLs 15773/0901-2
Aluminium/aluminium blister packs.
Pack size: 15, 30, 60, 90

HDPE bottles with white PP closures with induction sealing wad and desiccant (silica gel canister).
Bottle size: 100

For PLs 15773/0903-4
Aluminium/aluminium blister packs.
Pack size: 7, 15, 30, 60, 90

HDPE bottles with white PP closures with induction sealing wad and desiccant (silica gel canister).
Bottle size: 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Administration through gastric tube

1. Put the tablet into an appropriate syringe and fill the syringe with approximately 25 ml water and approximately 5 ml air. For some tubes, dispersion in 50 ml water is needed to prevent the pellets from clogging the tube.
2. Immediately shake the syringe for approximately 2 minutes to disperse the tablet.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe and position it with the tip pointing down. Immediately inject 5 – 10 ml into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip).
6. Turn the syringe with the tip down and immediately inject another 5 – 10 ml into the tube. Repeat this procedure until the syringe is empty.
7. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 5 and 6 if necessary to wash down any sediment left in the syringe. For some tubes, 50 ml water is needed.
Module 3

Patient Information Leaflet – text versions

Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0778-9)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Esomeprazole 20 mg and 40 mg gastro-resistant tablets
Esomeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Esomeprazole Tablets is and what it is used for
2. Before you take Esomeprazole Tablets
3. How to take Esomeprazole Tablets
4. Possible side effects
5. How to store Esomeprazole Tablets
6. Further information

1. WHAT ESOMEPRAZOLE TABLETS IS AND WHAT IT IS USED FOR

Esomeprazole Tablets contain a medicine called esomeprazole. This belongs to a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces.

Esomeprazole Tablets is used to treat the following conditions:
Adults and young people aged 12 years and above
- ‘Gastro-oesophageal reflux disease’ (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called ‘Helicobacter pylori’. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcers to heal.

Adults
- Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs).
- Esomeprazole Tablets can also be used to stop stomach ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
- Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole.

2. BEFORE YOU TAKE Esomeprazole Tablets

Do not take Esomeprazole Tablets if you
- are allergic (hypersensitive) to esomeprazole or any of the other ingredients of this medicine (listed in Section 6: Further information).
- are allergic to other proton pump inhibitor medicines.
- are taking a medicine containing nefilavir (used to treat HIV).

Do not take Esomeprazole Tablets if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Esomeprazole Tablets.
Take special care with Esomeprazole Tablets

Check with your doctor or pharmacist before taking Esomeprazole Tablets if you:
- have severe liver problems.
- have severe kidney problems.

Esomeprazole Tablets may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Esomeprazole Tablets or while you are taking it, talk to your doctor straight away:
- if you lose a lot of weight for no reason and have problems swallowing.
- if you get stomach pain or indigestion.
- if you begin to vomit food or blood.
- if you pass black stools (blood-stained faeces).

If you have been prescribed Esomeprazole Tablets “on demand” you should contact your doctor if your symptoms continue or change in character.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Esomeprazole Tablets can affect the way some medicines work and some medicines can have an effect on Esomeprazole Tablets.

Do not take Esomeprazole Tablets if you are taking a medicine containing nelﬁnavir (used to treat HIV).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Atazanavir (used to treat HIV).
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Esomeprazole Tablets.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Esomeprazole Tablets.
- Cisapride (used for indigestion and heartburn).
- Clopidogrel (used to prevent blood clots (thrombs)).

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Esomeprazole Tablets to treat ulcers caused by Helicobacter pylori infection, it is very important that you tell your doctor about any other medicines you are taking.

Taking Esomeprazole Tablets with food and drink

You can take your tablets with food or on an empty stomach.

Pregnancy and breast-feeding

Before taking Esomeprazole Tablets tell your doctor if you are pregnant or trying to get pregnant. Ask your doctor or pharmacist for advice before taking any medicine. As a precautionary measure, it is preferable to avoid the use of Esomeprazole Tablets during pregnancy.

It is unknown if esomeprazole passes into breast milk. Therefore, you should not take Esomeprazole Tablets if you are breast-feeding.
Driving and using machines

Esomeprazole Tablets is not likely to affect you being able to drive or use any tools or machines.

Important information about some of the ingredients of Esomeprazole Tablets

Esomeprazole Tablets contains sucrose and lactose, which are types of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE Esomeprazole Tablets:

Always take Esomeprazole Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Esomeprazole 20 mg gastro-resistant tablets are not recommended for the use in children less than 20 kg body weight.
- Esomeprazole 40 mg gastro-resistant tablets are not indicated for the use in children younger than 12 years.
- The experience of treatment with esomeprazole in infants younger than 1 year is limited and treatment is therefore not recommended.
- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

Method of administration
- You can take your tablets at any time of the day.
- You can take your tablets with food or on an empty stomach.
- Swallow your tablets whole with a drink of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you have trouble swallowing the tablets
- If you have trouble swallowing the tablets:
  - Put them into a glass of still (non-fizzy) water. Do not use any other liquids.
  - Stir until the tablets break up (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.
- If you cannot swallow at all, the tablet can be mixed with some water and put into a syringe. It can then be given to you through a tube directly into your stomach (‘gastric tube’).

Dosage
- Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.
- The usual doses are given below.

To treat heartburn caused by gastro-oesophageal reflux disease (GORD):

Adults and children aged 12 or above:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is one Esomeprazole 20 mg gastro-resistant tablet once a day.
- If your gullet has not been damaged, the usual dose is one Esomeprazole 20 mg gastro-resistant tablet each day. Once the condition has been controlled, your doctor may tell you to take your medicine as and when you need it, up to a maximum of one Esomeprazole 20 mg gastro-resistant tablet each day.
- If you have severe liver problems, your doctor may give you a lower dose.
To treat endoscopically proven erosive reflux oesophagitis
- Children with body weight 20 kg and above: the usual dose is 10 mg or 20 mg once daily for 8 weeks.
  (Other esomeprazole products are available for the treatment at a dose of 10 mg)

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:
- Adults and young people aged 12 or above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet twice a day for one week.
- Your doctor will also tell you to take antibiotics, for example amoxicillin and clarithromycin.

To treat stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day for 4 to 8 weeks.

To prevent stomach ulcers if you are taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):
- Adults aged 18 and above: the usual dose is one Esomeprazole 40 mg gastro-resistant tablet twice a day.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for. The maximum dose is 80 mg twice a day.

Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole:
- The usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks.

If you take more Esomeprazole Tablets than you should

If you take more Esomeprazole Tablets than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take Esomeprazole Tablets

If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose.
Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Esomeprazole Tablets can cause side effects, although not everybody gets them.

If you notice any of the following serious side effects, stop taking Esomeprazole Tablets and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be ‘Stevens-Johnson syndrome’ or ‘toxic epidermal necrolysis’.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare, affecting less than 1 in 1,000 people.
Other side effects include:

**Common (affects less than 1 in 10 people)**
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

**Uncommon (affects less than 1 in 100 people)**
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as “pins and needles”, feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how your liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.

**Rare (affects less than 1 in 1,000 people)**
- Blood problems such as a reduced number of white cells or platelets. This may cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste change.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation inside the mouth.
- An infection called “thrush” which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pain (arthralgia) or muscle pain (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

**Very rare (affects less than 1 in 10,000 people)**
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pain (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.
- Low levels of magnesium in the blood. This may cause weakness, being sick (vomiting), cramps, tremor and arrhythmias (heart rhythm disturbances).

Esomeprazole Tablets may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a severely reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you
must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test.

It is important for you to give information about your medication at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ESOMEPRAZOLE TABLETS

Keep out of the reach and sight of children.

Do not use Esomeprazole Tablets after the expiry date which is stated on the carton and blister/bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

Bottle: Shelf life after first opening: 100 days

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Esomeprazole Tablets contains:

- The active substance is esomeprazole. Esomeprazole gastro-resistant tablets come in two strengths containing 20 mg or 40 mg of esomeprazole (as esomeprazole magnesium).

- The other ingredients are: cellulose, microcrystalline; tcalc; lactose monohydrate; maize starch; macrogol 8,000; methacrylic acid - ethyl acrylate copolymer (1:1); sodium laurylsulfate; polysorbate 80; copovidone; crospovidone type A; sugar spheres (sucrose and maize starch); povidone; hypronellose; light magnesium oxide; magnesium stearate; dextyl phthalate; silica, colloidal anhydrous; titanium dioxide (E171); ethylcellulose; iron oxide red (E172); Opacode S-1-17823 black ink containing iron oxide black (E172), shellac, propylene glycol and ammonium hydroxide.

What Esomeprazole Tablets looks like and contents of the pack:

Esomeprazole 20 mg gastro-resistant tablets:
Brick red coloured, round shape, biconvex, film-coated tablet, imprinted with “20” on one side.

Esomeprazole 40 mg gastro-resistant tablets:
Brick red coloured, round shape, bevelled edge, biconvex, film-coated tablet, imprinted with “40” on one side.

Pack sizes: 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 100x1, 150

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany
**Manufacturer**  
Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, The Netherlands

OR*  
Merckle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany

OR*  
Teva Sante, Rue Belloctier, 89107 Sens, France

*This leaflet was last revised in July 2011*

PL 15773/0778-9

*Only the paragraph containing the details of the current batch release site will be included in the printed version of the PIL.*
Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0901-2)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Esomeprazole 20 mg and 40 mg gastro-resistant tablets

Esomeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT ESOMEPRAZOLE TABLETS IS AND WHAT IT IS USED FOR
2. BEFORE YOU TAKE Esomeprazole Tablets
3. How to take Esomeprazole Tablets
4. Possible side effects
5. How to store Esomeprazole Tablets
6. Further information

1. WHAT ESOMEPRAZOLE TABLETS IS AND WHAT IT IS USED FOR

Esomeprazole Tablets contains a medicine called esomeprazole. This belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

Esomeprazole Tablets is used to treat the following conditions:
- Adults and young people aged 12 years and above
  - 'Gastro-oesophageal reflux disease' (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
  - Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called 'Helicobacter pylori'. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Adults
  - Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs).
  - Esomeprazole Tablets can also be used to stop stomach ulcers from forming if you are taking NSAIDs.
  - Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
  - Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole.

2. BEFORE YOU TAKE Esomeprazole Tablets

Do not take Esomeprazole Tablets if you
- are allergic (hypersensitive) to esomeprazole or any of the other ingredients of this medicine (listed in Section 6. Further information).
- are allergic to other proton pump inhibitor medicines.
- are taking a medicine containing neflinavir (used to treat HIV).

Do not take Esomeprazole Tablets if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Esomeprazole Tablets.
Take special care with Esomeprazole Tablets

Check with your doctor or pharmacist before taking Esomeprazole Tablets if you:
- have severe liver problems.
- have severe kidney problems.

Esomeprazole Tablets may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Esomeprazole Tablets or while you are taking it, talk to your doctor straight away:
- if you lose a lot of weight for no reason and have problems swallowing.
- if you get stomach pain or indigestion.
- if you begin to vomit food or blood.
- if you pass black stools (blood-stained faeces).

If you have been prescribed Esomeprazole Tablets "on demand" you should contact your doctor if your symptoms continue or change in character.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Esomeprazole Tablets can affect the way some medicines work and some medicines can have an effect on Esomeprazole Tablets.

Do not take Esomeprazole Tablets if you are taking a medicine containing aefinavir (used to treat HIV).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Atazanavir (used to treat HIV).
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Esomeprazole Tablets.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Esomeprazole Tablets.
- Cisapride (used for indigestion and heartburn).
- Clopidogrel (used to prevent blood clots (thrombi))

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Esomeprazole Tablets to treat ulcers caused by Helicobacter pylori infection, it is very important that you tell your doctor about any other medicines you are taking.

Taking Esomeprazole Tablets with food and drink

You can take your tablets with food or on an empty stomach.

Pregnancy and breast-feeding

Before taking Esomeprazole Tablets tell your doctor if you are pregnant or trying to get pregnant. Ask your doctor or pharmacist for advice before taking any medicine. As a precautionary measure, it is preferable to avoid the use of Esomeprazole Tablets during pregnancy.

It is unknown if esomeprazole passes into breast milk. Therefore, you should not take Esomeprazole Tablets if you are breast-feeding.
Driving and using machines

Esomeprazole Tablets is not likely to affect you being able to drive or use any tools or machines.

Important information about some of the ingredients of Esomeprazole Tablets

Esomeprazole Tablets contains sucrose and lactose, which are types of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE Esomeprazole Tablets

Always take Esomeprazole Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Esomeprazole 20 mg gastro-resistant tablets are not recommended for the use in children less than 20 kg body weight.
- Esomeprazole 40 mg gastro-resistant tablets are not indicated for the use in children younger than 12 years.
- The experience of treatment with esomeprazole in infants younger than 1 year is limited and treatment is therefore not recommended.
- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

Method of administration

- You can take your tablets at any time of the day.
- You can take your tablets with food or on an empty stomach.
- Swallow your tablets whole with a drink of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you have trouble swallowing the tablets

- If you have trouble swallowing the tablets:
  - Put them into a glass of still (non-fizzy) water. Do not use any other liquids.
  - Stir until the tablets break up (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.
  - If you cannot swallow at all, the tablet can be mixed with some water and put into a syringe. It can then be given to you through a tube directly into your stomach ("gastric tube").

Dosage

- Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.
- The usual doses are given below.

To treat heartburn caused by gastro-oesophageal reflux disease (GORD):

Adults and children aged 12 or above:

- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is one Esomeprazole 20 mg gastro-resistant tablet once a day.
- If your gullet has not been damaged, the usual dose is one Esomeprazole 20 mg gastro-resistant tablet each day. Once the condition has been controlled, your doctor may tell you to take your medicine as and when you need it, up to a maximum of one Esomeprazole 20 mg gastro-resistant tablet each day.
- If you have severe liver problems, your doctor may give you a lower dose.
To treat endoscopically proven erosive reflux oesophagitis
- Children with body weight 20 kg and above: the usual dose is 10 mg or 20 mg once daily for 8 weeks.
  (Other esomeprazole products are available for the treatment at a dose of 10 mg.)

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:
- Adults and young people aged 12 or above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet twice a day for one week.
- Your doctor will also tell you to take antibiotics, for example amoxicillin and clarithromycin.

To treat stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day for 4 to 8 weeks.

To prevent stomach ulcers if you are taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):
- Adults aged 18 and above: the usual dose is one Esomeprazole 40 mg gastro-resistant tablet twice a day.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for. The maximum dose is 80 mg twice a day.

Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole:
- The usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks.

If you take more Esomeprazole Tablets than you should

If you take more Esomeprazole Tablets than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take Esomeprazole Tablets

If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose.
Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Esomeprazole Tablets can cause side effects, although not everybody gets them.

If you notice any of the following serious side effects, stop taking Esomeprazole Tablets and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be ‘Stevens-Johnson syndrome’ or ‘toxic epidermal necrolysis’.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare, affecting less than 1 in 1,000 people.
Other side effects include:

**Common (affects less than 1 in 10 people)**
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

**Uncommon (affects less than 1 in 100 people)**
- Swelling of the feet and ankles.
- Dizziness, tingling feelings such as “pins and needles”, feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how your liver is working.
- Skin rash, humpy rash (hives) and itchy skin.

**Rare (affects less than 1 in 1,000 people)**
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation inside the mouth.
- An infection called “thrush” which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pain (arthralgia) or muscle pain (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

**Very rare (affects less than 1 in 10,000 people)**
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeming, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pain (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.
- Low levels of magnesium in the blood. This may cause weakness, being sick (vomiting), cramps, tremor and arrhythmias (heart rhythm disturbances).

Esomeprazole Tablets may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a severely reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you
must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test.

It is important for you to give information about your medication at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ESOMEPRAZOLE TABLETS

Keep out of the reach and sight of children.

Do not use Esomeprazole Tablets after the expiry date which is stated on the carton and blister/bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

Bottle: Shelf life after first opening: 100 days

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Esomeprazole Tablets contains

- The active substance is esomeprazole. Esomeprazole gastro-resistant tablets come in two strengths containing 20 mg or 40 mg of esomeprazole (as esomeprazole magnesium).
- The other ingredients are: cellulose, microcrystalline; talc; lactose monohydrate; maize starch; macrogol 8.000; methacrylic acid - ethyl acrylate copolymer (1:1); sodium laurylsulfate; polysorbate 80; copovidone; crospovidone type A; sugar spheres (sucrose and maize starch); povidone; hypromellose; light magnesium oxide; magnesium stearate; diethyl phthalate; silica, colloidal anhydrous; titanium dioxide (E171); ethylcellulose; iron oxide red (E172); Opacode S-1-17823 black ink containing iron oxide black (E 172), shellac, propylene glycol and ammonium hydroxide.

What Esomeprazole Tablets looks like and contents of the pack

Esomeprazole 20 mg gastro-resistant tablets:
Brick red coloured, round shape, biconvex, film-coated tablet, imprinted with “20” on one side.

Esomeprazole 40 mg gastro-resistant tablets:
Brick red coloured, round shape, bevelled edge, biconvex, film-coated tablet, imprinted with “40” on one side.

Pack sizes: 15, 30, 60, 90, 100

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany
Manufacturer
Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, The Netherlands
OR*
Merckle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany
OR*
Teva Sante, Rue Bellocq, 89107 Sens, France

This leaflet was last revised in July 2011

PL 15773/0901-902

* Only the paragraph containing the details of the current batch release site will be included in the printed version of the PIL
Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0903-4)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Esomeprazole 20 mg and 40 mg gastro-resistant tablets

Esomeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Esomeprazole Tablets is and what it is used for
2. Before you take Esomeprazole Tablets
3. How to take Esomeprazole Tablets
4. Possible side effects
5. How to store Esomeprazole Tablets
6. Further information

1. WHAT ESOMEPRAZOLE TABLETS IS AND WHAT IT IS USED FOR

Esomeprazole Tablets contains a medicine called esomeprazole. This belongs to a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces.

Esomeprazole Tablets is used to treat the following conditions:

Adults and young people aged 12 years and above
- ‘Gastro-oesophageal reflux disease’ (GORD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called ‘Helicobacter pylori’. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

Adults
- Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs).
  - Esomeprazole Tablets can also be used to stop stomach ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
- Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole.

2. BEFORE YOU TAKE Esomeprazole Tablets

Do not take Esomeprazole Tablets if you

- are allergic (hypersensitive) to esomeprazole or any of the other ingredients of this medicine (listed in Section 6: Further information).
- are allergic to other proton pump inhibitor medicines.
- are taking a medicine containing neflinavir (used to treat HIV).

Do not take Esomeprazole Tablets if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Esomeprazole Tablets.
Take special care with Esomeprazole Tablets

Check with your doctor or pharmacist before taking Esomeprazole Tablets if you:
- have severe liver problems.
- have severe kidney problems.

Esomeprazole Tablets may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Esomeprazole Tablets or while you are taking it, talk to your doctor straight away:
- if you lose a lot of weight for no reason and have problems swallowing.
- if you get stomach pain or indigestion.
- if you begin to vomit food or blood.
- if you pass black stools (blood-stained faeces).

If you have been prescribed Esomeprazole Tablets "on demand" you should contact your doctor if your symptoms continue or change in character.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Esomeprazole Tablets can affect the way some medicines work and some medicines can have an effect on Esomeprazole Tablets.

Do not take Esomeprazole Tablets if you are taking a medicine containing neflinavir (used to treat HIV).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Atazanavir (used to treat HIV).
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking Esomeprazole Tablets.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Esomeprazole Tablets.
- Cisapride (used for indigestion and heartburn).
- Clopidogrel (used to prevent blood clots (thrombi)).

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Esomeprazole Tablets to treat ulcers caused by Helicobacter pylori infection, it is very important that you tell your doctor about any other medicines you are taking.

Taking Esomeprazole Tablets with food and drink

You can take your tablets with food or on an empty stomach.

Pregnancy and breast-feeding

Before taking Esomeprazole Tablets tell your doctor if you are pregnant or trying to get pregnant. Ask your doctor or pharmacist for advice before taking any medicine. As a precautionary measure, it is preferable to avoid the use of Esomeprazole Tablets during pregnancy.

It is unknown if esomeprazole passes into breast milk. Therefore, you should not take Esomeprazole Tablets if you are breast-feeding.
Driving and using machines

Esomeprazole Tablets is not likely to affect you being able to drive or use any tools or machines.

Important information about some of the ingredients of Esomeprazole Tablets

Esomeprazole Tablets contains sucrose and lactose, which are types of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE Esomeprazole Tablets

Always take Esomeprazole Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Esomeprazole 20 mg gastro-resistant tablets are not recommended for the use in children less than 20 kg body weight.
- Esomeprazole 40 mg gastro-resistant tablets are not indicated for the use in children younger than 12 years.
- The experience of treatment with esomeprazole in infants younger than 1 year is limited and treatment is therefore not recommended.
- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

Method of administration
- You can take your tablets at any time of the day.
- You can take your tablets with food or on an empty stomach.
- Swallow your tablets whole with a drink of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you have trouble swallowing the tablets
- If you have trouble swallowing the tablets:
  - Put them into a glass of still (non-fizzy) water. Do not use any other liquids.
  - Stir until the tablets break up (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
  - To make sure that you have drunk all of the medicine, raise the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.
  - If you cannot swallow at all, the tablet can be mixed with some water and put into a syringe. It can then be given to you through a tube directly into your stomach ("gastric tube").

Dosage
- Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.
- The usual doses are given below.

To treat heartburn caused by gastro-oesophageal reflux disease (GORD):

Adults and children aged 12 or above:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is one Esomeprazole 20 mg gastro-resistant tablet once a day.
- If your gullet has not been damaged, the usual dose is one Esomeprazole 20 mg gastro-resistant tablet each day. Once the condition has been controlled, your doctor may tell you to take your medicine as and when you need it, up to a maximum of one Esomeprazole 20 mg gastro-resistant tablet each day.
- If you have severe liver problems, your doctor may give you a lower dose.
To treat endoscopically proven erosive reflux oesophagitis
- Children with body weight 20 kg and above: the usual dose is 10 mg or 20 mg once daily for 8 weeks.
  (Other esomeprazole products are available for the treatment at a dose of 10 mg.)

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:
- Adults and young people aged 12 or above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet twice a day for one week.
- Your doctor will also tell you to take antibiotics, for example amoxicillin and clarithromycin.

To treat stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day for 4 to 8 weeks.

To prevent stomach ulcers if you are taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one Esomeprazole 20 mg gastro-resistant tablet once a day.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):
- Adults aged 18 and above: the usual dose is one Esomeprazole 40 mg gastro-resistant tablet twice a day.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for. The maximum dose is 80 mg twice a day.

Prolonged treatment after prevention of rebleeding of ulcers with intravenous Esomeprazole:
- The usual dose is one Esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks.

If you take more Esomeprazole Tablets than you should

If you take more Esomeprazole Tablets than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take Esomeprazole Tablets

If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Esomeprazole Tablets can cause side effects, although not everybody gets them.

If you notice any of the following serious side effects, stop taking Esomeprazole Tablets and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare, affecting less than 1 in 1,000 people.
Other side effects include:

Common (affects less than 1 in 10 people)
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon (affects less than 1 in 100 people)
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how your liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.

Rare (affects less than 1 in 1,000 people)
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation inside the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pain (arthritis) or muscle pain (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

Very rare (affects less than 1 in 10,000 people)
- Changes in blood count including agranulocytosis (lack of white blood cells)
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pain (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.
- Low levels of magnesium in the blood. This may cause weakness, being sick (vomiting), cramps, tremor and arrhythmias (heart rhythm disturbances).

Esomeprazole Tablets may in very rare cases affect the white blood cells leading to immune deficiency.
If you have an infection with symptoms such as fever with a severely reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you
must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test.
It is important for you to give information about your medication at this time.

Do not be concerned by this list of possible side effects. You may not get any of them.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ESOMEPRAZOLE TABLETS

Keep out of the reach and sight of children.

Do not use Esomeprazole Tablets after the expiry date which is stated on the carton and blister/bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

Bottle: Shelf life after first opening: 100 days

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Esomeprazole Tablets contains

- The active substance is esomeprazole. Esomeprazole gastro-resistant tablets come in two strengths containing 20 mg or 40 mg of esomeprazole (as esomeprazole magnesium).
- The other ingredients are: cellulose, microcrystalline, talc, lactose monohydrate, maize starch, macrogol 8000; methacrylic acid - ethyl acrylate copolymer (1:1); sodium laurilsulfate; polysorbate 80; copovidone; crospovidone type A; sugar spheres (sucrose and maize starch); povidone, hypromellose; light magnesium oxide; magnesium stearate; diethyl phthalate; silica, colloidal anhydrous; titanium dioxide (E171); ethylcellulose; iron oxide red (E172); Opacode S-1-17823 black ink containing iron oxide black (E172), shellac, propylene glycol and ammonium hydroxide.

What Esomeprazole Tablets looks like and contents of the pack

Esomeprazole 20 mg gastro-resistant tablets:
Brick red coloured, round shape, biconvex, film-coated tablet, imprinted with “20” on one side.

Esomeprazole 40 mg gastro-resistant tablets:
Brick red coloured, round shape, bevelled edge, biconvex, film-coated tablet, imprinted with “40” on one side.

Pack sizes: 7, 15, 30, 60, 90, 100

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany
Manufacturer
Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, The Netherlands

OR*

Merkle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany

OR*

Teva Sante, Rue Bellocier, 89107 Sens, France

This leaflet was last revised in July 2011

PL 15773/0903-4

* Only the paragraph containing the details of the current batch release site will be included in the printed version of the PIL
Module 4

Labelling – text versions

Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0778-9)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| (Carton Box/Bottle Label) |

1. NAME OF THE MEDICINAL PRODUCT
   Esomeprazole 20/40 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
   Each gastro-resistant tablet contains 20/40 mg Esomeprazole (as esomeprazole magnesium).

3. LIST OF EXCIPIENTS
   Contains lactose and sucrose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS
   gastro-resistant tablet
   7 gastro-resistant tablets
   14 gastro-resistant tablets
   15 gastro-resistant tablets
   28 gastro-resistant tablets
   30 gastro-resistant tablets
   50 gastro-resistant tablets
   56 gastro-resistant tablets
   60 gastro-resistant tablets
   90 gastro-resistant tablets
   98 gastro-resistant tablets
   100 gastro-resistant tablets
   100ml gastro-resistant tablets
   150 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
   Oral use
   Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
   Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
   EXP: Discard 100 days after first opening of the bottle
9. **SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from light and moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**
    ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm

12. **MARKETING AUTHORISATION NUMBER(S)**
    PL 15773/0778-9

13. **BATCH NUMBER**
    Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**
    POM

15. **INSTRUCTIONS ON USE**
    Use as directed by the doctor

16. **INFORMATION IN BRAILLE**
    Esomeprazole 20/40 mg gastro-resistant tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 20 mg gastro-resistant tablets
Or
Esomeprazole 40 mg gastro-resistant tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0901-2)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| {Carton Box/Bottle Label} |

1. **NAME OF THE MEDICINAL PRODUCT**
   Esomeprazole 20/40 mg gastro-resistant tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   Each gastro-resistant tablet contains 20/40 mg Esomeprazole (as esomeprazole magnesium).

3. **LIST OF EXCipients**
   Contains lactose and sucrose. See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**
   gastro-resistant tablet
   - 15 gastro-resistant tablets
   - 30 gastro-resistant tablets
   - 60 gastro-resistant tablets
   - 90 gastro-resistant tablets
   - 100 gastro-resistant tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   EXP
   Discard 100 days after first opening of the bottle

9. **SPECIAL STORAGE CONDITIONS**
   Store in the original package in order to protect from light and moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm

12. MARKETING AUTHORISATION NUMBER(S)

PL 15773/0901-2

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Esomeprazole 20/40 mg gastro-resistant tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 20 mg gastro-resistant tablets

Or

Esomeprazole 40 mg gastro-resistant tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0903-4)

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| (Carton Box/Bottle Label) |

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 20/40 mg gastro-resistant tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20/40 mg Esomeprazole (as esomeprazole magnesium).

3. LIST OF EXCIPIENTS

Contains lactose and sucrose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

- gastro-resistant tablet
  - 7 gastro-resistant tablets
  - 15 gastro-resistant tablets
  - 30 gastro-resistant tablets
  - 60 gastro-resistant tablets
  - 90 gastro-resistant tablets
  - 100 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Discard 100 days after first opening of the bottle

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

ratiopharm GmbH, Graf-Arco-Straße 3, D-89079 Ulm

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 15773/0903-4

13. **BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

Esomeprazole 20/40 mg gastro-resistant tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole 20 mg gastro-resistant tablets

Or

Esomeprazole 40 mg gastro-resistant tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ratiopharm GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Ratiopharm GmbH Marketing Authorisations for the medicinal products Esomeprazole 20 mg and 40 mg gastro-resistant tablets (PL 15773/0778-9, 0901-2 and 0903-4; UK/H/2916 & 4424-5/001-2/DC) on 24th August 2011. The products are prescription-only medicines.

These are generic applications for Esomeprazole 20 mg and 40 mg gastro-resistant tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Nexium® 20 mg and 40 mg tablets (PL 17901/0068 and 0069), authorised to AstraZeneca AB on 27th July 2000, through incoming Mutual Recognition procedures [SE/H/0211/001-2/MR] where Sweden was the Reference Member State (RMS). The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired. The European originator products, Nexium® 20 mg, 40 mg enterotabletter, were first authorised to AstraZeneca AB in Sweden on 10th March 2000.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Ratiopharm GmbH applied for Marketing Authorisations for Esomeprazole 20 mg and 40 mg gastro-resistant tablets in Austria, Bulgaria, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain and Sweden.

Esomeprazole 20 mg and 40 mg gastro-resistant tablets are indicated for the following:

- Gastro-oesophageal Reflux Disease (GORD):
  - treatment of erosive reflux oesophagitis
  - long-term management of patients with healed oesophagitis to prevent relapse
  - symptomatic treatment of gastro-oesophageal reflux disease (GORD)
- In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and:
  - healing of Helicobacter pylori associated duodenal ulcer and
  - prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers
- Patients requiring continued NSAID therapy:
  - healing of gastric ulcers associated with NSAID therapy
  - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk
- Treatment of Zollinger Ellison Syndrome
- Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers

The active ingredient, esomeprazole, belongs to the pharmacotherapeutic group of ‘proton pump inhibitors’ (ATC code – A02BC05). Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H⁺K⁺-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90 % when measured 6-7 hours after dosing on day five. After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a series of bioequivalence studies comparing the pharmacokinetic profile of the test product, Esomeprazole 40 mg gastro-resistant tablets, to that of the reference product, Nexium® MUPS 40 mg tablets (AstraZeneca, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a detailed Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Esomeprazole 20 mg gastro-resistant tablets  
Esomeprazole 40 mg gastro-resistant tablets |
| Name(s) of the active substance(s) (INN) | Esomeprazole |
| Pharmacotherapeutic classification (ATC code) | Proton pump inhibitors  
(A02BC05) |
| Pharmaceutical form and strength(s) | Gastro-resistant tablets  
20 mg, 40 mg |
| Reference numbers for the Decentralised Procedure | UK/H/2916 & 4424-5/001-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/2916/001-2/DC: AT, BG, DE, DK, EE, ES, FI, FR, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE and SK  
UK/H/4424/001-2/DC: DE  
UK/H/4425/001-2/DC: DE |
| Marketing Authorisation Number(s) | PL 15773/0778-9, 0901-2 and 0903-4 |
| Name and address of the authorisation holder | Ratiopharm GmbH,  
Graf-Arco-Strasse 3,  
D-89079 Ulm |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Esomeprazole

Nomenclature:

INN: Esomeprazole magnesium
Compendial name: Magnesium bis[5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphynyl]-IH-benzimidazolide]
Chemical names: i) 5-methoxy-2-{[(S)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfonyl} benzimidazole magnesium (2:1)
ii) Bis[5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-IHbenzimidazolato]magnesium

Structure:

\[
\text{Mg}^2+\left[\begin{array}{c}
\text{MeO} \\
\text{N} \\
\text{S} \\
\text{CH}_3 \\
\text{OMe} \\
\text{CH}_3 \\
\end{array}\right]
\]

Molecular formula: \( C_{34}H_{36}MgN_6O_6S_2 \)
Molecular weight: 713.1 g/mol
CAS No: 161973-10-0
Physical form: White to pale-cream coloured powder
Solubility: Soluble in N,N-Dimethyl formamide and slightly soluble in methanol
Chirality: Omeprazole contains one chiral centre. The S-isomer is manufactured and isolated as the magnesium salt

The active substance, Esomeprazole magnesium, is not the subject of a European Pharmacopeia (Ph. Eur.) or British Pharmacopeia (B.P.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.
The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 18-month retest period that has been applied, when the active substance is stored at 2-8°C.

**MEDICINAL PRODUCT**

**Description and Composition**

Esomeprazole 20 mg and 40 mg gastro-resistant tablets are presented as brick-red coloured, round, biconvex, film-coated tablets imprinted with ‘20’ / ‘40’ on one side. Each tablet contains 20 mg or 40 mg of the active ingredient, esomeprazole, as esomeprazole magnesium.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, talc, lactose monohydrate, maize starch, macrogol 8000, methacrylic acid - ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80, copovidone, crospovidone type A, sugar spheres (sucrose and maize starch), povidone, hydroxypropyl methylcellulose, magnesium stearate, diethyl phthalate, colloidal anhydrous silica, titanium dioxide (E171), ethylcellulose and iron oxide red (E172). ‘Opacode S-1-17823 black ink’ used for imprinting the tablets contains iron oxide black (E172), shellac, propylene glycol and ammonium hydroxide. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Opacode S-1-17823 black ink, which is controlled to satisfactory in-house specifications, and iron oxide red (E172), which complies with the EU colouring regulation 95/45/EC. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop stable, generic medicinal products, bioequivalent to the reference products, Nexium® 20 mg and 40 mg tablets (PL 17901/0068 and 0069, AstraZeneca AB).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

**Finished product specification**

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The medicinal products are licensed for marketing in aluminium/aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 and 100x1 (PLs 15773/0778-9); 15, 30, 60 and 90 (PLs 15773/0901-2); and 7, 15, 30, 60 and 90 (PLs 15773/0903-4). The products are also licensed in HDPE bottles of 100 and, for PLs 15773/0778-9 only, 150 film-coated tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-lives of 2 years for the blister and HDPE bottle packs. Once opened, the shelf-life of the HDPE bottles is 100 days. Storage instructions are ‘Store in the original package in order to protect from light and moisture’.

**Quality Overall Summary**

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The labelling texts fulfil the statutory requirements for Braille. The user-testing of the PIL text has been evaluated and is accepted. The MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Esomeprazole 20 mg and 40 mg gastro-resistant tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole, a widely used and well-known active substance. The overview, dated January 2010, cites 15 references from the published literature dated up to year 2010. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Nexium® 20 mg and 40 mg tablets (PL 17901/0068 and 0069, AstraZeneca AB).

There are no objections to approval of Esomeprazole 20 mg and 40 mg gastro-resistant tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Esomeprazole 20 mg and 40 mg gastro-resistant tablets are indicated for the following:

- Gastro-oesophageal Reflux Disease (GORD):
  - treatment of erosive reflux oesophagitis
  - long-term management of patients with healed oesophagitis to prevent relapse
  - symptomatic treatment of gastro-oesophageal reflux disease (GORD)
- In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and:
  - healing of Helicobacter pylori associated duodenal ulcer and
  - prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers
- Patients requiring continued NSAID therapy:
  - healing of gastric ulcers associated with NSAID therapy
  - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk
- Treatment of Zollinger Ellison Syndrome
- Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of esomeprazole is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of esomeprazole is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications. Esomeprazole is the S-isomer of omeprazole. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
Pharmacokinetics – bioequivalence study

The applications are supported by 3 bioequivalence studies presented by the applicant comparing the pharmacokinetic profile of the test product, Esomeprazole 40 mg gastro-resistant tablets (AstraZeneca, Germany). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products. The UK reference product, Nexium® MUPS 40 mg tablets, is considered to be equivalent to the clinical reference product, Nexium® MUPS 40 mg tablets (AstraZeneca, Germany).

The primary pharmacokinetic parameters for the studies were C\text{max}, \text{AUC}_{0-t}, and \text{AUC}_{0-\infty}.

Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed C\text{max}, \text{AUC}_{0-t}, and \text{AUC}_{0-\infty} for esomeprazole.

Study A – fasted, single dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in 56 healthy adult human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 13 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 16.0 hours after administration of test or reference product. Plasma levels of esomeprazole were quantified by a validated LC-MS method.

Results:

56 subjects were enrolled in the study; 54 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 2 subjects was satisfactorily justified.

Safety - A total of 22 post-dose adverse events were recorded in the study: 11 events for subjects dosed with test product and 11 events for subjects dosed with reference product. All events were mild to moderate in severity having possible or no relationship to the study drug. 20 events resolved without sequelae. There were no new safety issues raised during the study.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio (Y/X) %</td>
<td></td>
</tr>
<tr>
<td>C\text{max} (ng/ml)</td>
<td>93.84</td>
<td>85.59-102.88%</td>
</tr>
<tr>
<td>\text{AUC}_{0-t} (ng.h/ml)</td>
<td>106.36</td>
<td>98.80-114.50%</td>
</tr>
<tr>
<td>\text{AUC}_{0-\infty} (ng.h/ml)</td>
<td>106.47</td>
<td>98.93-114.58%</td>
</tr>
</tbody>
</table>

C\text{max} maximum plasma concentration
\text{AUC}_{0-t} area under the plasma concentration-time curve from time zero to t hours
\text{AUC}_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
Conclusion

Bioequivalence has been demonstrated between the test and reference products for a single-dose study conducted under fasting conditions.

Study B – fed, single dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in 56 healthy adult human subjects under fed conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period, 30 minutes after initiation of a standardised, high-fat, high-calorie breakfast. Identical meal plans were provided to the subjects at set periods during the study. A satisfactory washout period of 4 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of esomeprazole were quantified by a validated LC-MS/MS method.

Results:

56 subjects were enrolled in the study; 51 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 5 subjects was satisfactorily justified.

Safety - A total of 7 post-dose adverse events were recorded in the study. All events were mild to moderate in severity having possible or unlikely relationship to the study drug. All events resolved without sequelae. There were no new safety issues raised during the study.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for esomeprazole for a randomised, two-period, two-treatment, single-dose crossover study between the test and reference products. n=51 healthy subjects, dosed fed; t=24 hours. Wash-out period: 4 days.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio (Y/X) %</td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>107.79</td>
<td>100.02-116.16%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng.h/ml)</td>
<td>112.16</td>
<td>105.45-119.29%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng.h/ml)</td>
<td>112.24</td>
<td>105.57-119.32%</td>
</tr>
</tbody>
</table>

\( C_{\text{max}} \) maximum plasma concentration
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity

Conclusion

Bioequivalence has been demonstrated between the test and reference products for a single-dose study conducted under fed conditions.
**Study C – fasted, multiple dose**

This was an open-label, randomised, two-period, two-sequence, two-treatment, multiple-dose crossover bioequivalence study conducted in 44 healthy adult human subjects under fasting conditions. Subjects were fasted overnight at least 10 hours before the morning dose and for 4 hours post-dose from day 01 to day 07. Subjects were dosed with the test or the reference product in each period as determined by the randomization schedule. Identical meal plans were provided to the subjects at set periods during the study. A satisfactory washout period of 6 days was maintained between the dosing phases in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of esomeprazole were quantified by a validated LC-MS method.

**Results:**

44 subjects were enrolled in the study; 38 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 6 subjects was satisfactorily justified.

**Safety** - A total of 49 post-dose adverse events were recorded in the study: 31 events for subjects dosed with test product and 18 events for subjects dosed with reference product. All events were mild to moderate in severity having possible/remote/no relationship to the study drug. All events resolved without sequelae.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio (Y/X) %</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>93.67</td>
<td>89.70-97.82%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>99.17</td>
<td>94.81-103.73%</td>
</tr>
</tbody>
</table>

**Conclusion**

Bioequivalence has been demonstrated between the test and reference products for a multiple-dose study conducted under fasting conditions.

**Discussion on Bioequivalence**

The results of the bioequivalence study show that Esomeprazole 40 mg gastro-resistant tablets (test) and Nexium® MUPS 40 mg tablets - AstraZeneca, Germany (reference) are bioequivalent, as the confidence intervals for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> for esomeprazole fall within the acceptance criteria ranges of 80.00-125.00%, in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Esomeprazole 20 mg gastro-resistant tablets. As Esomeprazole 20 mg and 40 mg gastro-resistant tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence”
(CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 40 mg strength can be extrapolated to the 20 mg strength tablets.

Clinical efficacy
No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of esomeprazole is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of esomeprazole is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet
The final PIL texts are in line with the approved SmPCs and are satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling
The labelling texts are satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview, dated January 2010, cites 27 references from the published literature dated up to year 2007. The CV of the clinical expert has been supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Esomeprazole 20 mg and 40 mg gastro-resistant tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Esomeprazole 40 mg gastro-resistant tablets and the reference product, Nexium® MUPS 40 mg tablets (AstraZeneca, Germany). The UK reference product, Nexium® 40 mg tablets, is considered to be equivalent to the clinical reference product, Nexium® MUPS 40 mg tablets (AstraZeneca, Germany).

As the proposed products, Esomeprazole 20 mg and 40 mg gastro-resistant tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 40 mg strength were extrapolated to the 20 mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the UK reference products and are satisfactory.

The PIL text is in line with the SmPCs and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Esomeprazole 20 mg and 40 mg gastro-resistant tablets are generic versions of the reference products, Nexium® 20 mg and 40 mg tablets (AstraZeneca AB). Extensive clinical experience with esomeprazole is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
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<tr>
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