Public Assessment Report

Decentralised Procedure

Omeprazole 10 mg Gastro-resistant Capsules
Omeprazole 20 mg Gastro-resistant Capsules

Procedure No: UK/H/4500/001-2/DC

UK Licence No: PL 04416/1224-5

Sandoz Limited
Lay summary

On 02 March 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Sandoz Limited for the medicinal products Omeprazole 10 mg and 20 mg Gastro-resistant Capsules (PL 04416/1224-5; UK/H/4500/001-2/DC). Omeprazole 10 mg Gastro-resistant Capsules is a pharmacy (P) medicine, available only from pharmacies under the supervision of a pharmacist. Omeprazole 20 mg Gastro-resistant Capsules is a prescription-only medicine (POM). The products are used in adults for the short-term treatment of reflux symptoms (for example, heartburn and acid regurgitation). Reflux is the backflow of acid from the stomach into the gullet ‘foodpipe’, which may become inflamed and painful. This may cause symptoms such as a painful burning sensation in the chest rising up to the throat (heartburn) and a sour taste in the mouth (acid regurgitation).

The active ingredient, omeprazole, belongs to a group of medicines called ‘proton pump inhibitors’ that work by reducing the amount of acid that the stomach produces.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Omeprazole 10 mg and 20 mg Gastro-resistant Capsules; outweigh the risks and Marketing Authorisations were granted.
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Module 6: Steps taken after initial procedure
Module 1
Information about the initial procedure

| Product Names | UK/H/4500/001/DC: Omeprazole 10 mg Gastro-resistant Capsules  
|               | UK/H/4500/002/DC: Omeprazole 20 mg Gastro-resistant Capsules |
| Type of Applications | Generic, Article 10(1) |
| Active Substance | Omeprazole |
| Form | Gastro-resistant capsules |
| Strengths | 10 mg and 20 mg |
| MA Holder | Sandoz Limited  
|           | Frimley Business Park  
|           | Frimley  
|           | Camberley  
|           | Surrey  
|           | GU16 7SR  
|           | United Kingdom |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | Belgium, Bulgaria, Estonia, France, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Poland, Portugal, Romania and Slovak Republic |
| Procedure Numbers | UK/H/4500/001-2/DC |
| Timetable | Day 210 – 02 February 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Omeprazole 10 mg Gastro-resistant Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant capsule, hard contains 10mg of omeprazole.

   Excipient(s):
   Each 10 mg gastro-resistant capsule, hard contains 58.5 mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant capsule, hard (Gastro-resistant capsule)

   Light brown cap, light brown body, each imprinted with “OME 10” containing dull yellowish, brown granules

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Omeprazole 10 mg Gastro-resistant Capsules are indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

4.2 Posology and method of administration

   Posology in adults
   The recommended dose is 20 mg once daily for 14 days.

   It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms.

   The majority of patients achieve complete relief of heartburn within 7 days. Once complete relief of symptoms has occurred, treatment should be discontinued.

   Special populations
   Impaired renal function
   Dose adjustment is not needed in patients with impaired renal function (see section 5.2).

   Impaired hepatic function
   Patients with impaired hepatic function should be advised by a doctor before taking Omeprazole 10 mg Gastro-resistant Capsules (see section 5.2).

   Elderly (> 65 years old)
   Dose adjustment is not needed in the elderly (see section 5.2).

   Paediatric population
   This medicinal product should not be used in children and adolescents under the age of 18 years.

   Method of administration
   It is recommended to take Omeprazole 10 mg Gastro-resistant Capsules in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

   For patients with swallowing difficulties
   Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water.
Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients.

Omeprazole like other proton pump inhibitors must 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 melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

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

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, 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 omeprazole and clopidogrel should be discouraged.

Omeprazole 10 mg Gastro-resistant Capsules contain lactose. Therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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).

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any ‘over-the-counter’ (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should be instructed to consult a doctor if:

- They have had previous gastric ulcer or gastrointestinal surgery
- They are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients should not take omeprazole as a preventative medication.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

*Nelfinavir, atazanavir*

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75-90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg
to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. 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
to atazanavir 300 mg/ritonavir 100 mg once daily.

**Digoxin**

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the
bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should
be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring
digoxin should be then be reinforced.

**Clopidogrel**

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.

**Other active substances**

The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and
thus clinical efficacy may be impaired. For posaconazol and erlotinib concomitant use should be
avoided.

**Active substances metabolised by CYP2C19**

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus,
the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and
the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other
vitamin K antagonists, cilostazol, diazepam and phenytoin.

**Cilostazol**

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and
AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69%
respectively.

**Phenytoin**

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating
omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose
adjustment should occur upon ending omeprazole treatment.

**Unknown mechanism**

**Saquinavir**

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma
levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected
patients.

**Tacrolimus**

Concomitant administration of omeprazole has been reported to increase the serum levels of
tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine
clearance) should be performed, and dosage of tacrolimus adjusted if needed.

**Effects of other active substances on the pharmacokinetics of omeprazole**

**Inhibitors of CYP2C19 and/or CYP3A4**

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit
CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole
serum levels by decreasing omeprazole’s rate of metabolism. Concomitant voriconazole treatment
resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been
well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment
should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

**Inducers of CYP2C19 and/or CYP3A4**
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John’s wort) may lead to decreased omeprazole serum levels by increasing omeprazole’s rate of metabolism.

4.6 **Fertility, Pregnancy and lactation**

**Pregnancy**
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

**Lactation**
Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

**Fertility**
There are no data on the effect of omeprazole on human fertility. Fertility was unaffected following omeprazole treatment in animal studies.

4.7 **Effects on ability to drive and use machines**
Omeprazole 10 mg Gastro-resistant Capsules is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 **Undesirable effects**
The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), 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), Not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>SOC/frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Agranulocytosis, pancytopenia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Hypomagnesaemia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Rare:</td>
<td>Agitation, confusion, depression</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Aggression, hallucinations</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Headache</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Dizziness, paraesthesia, somnolence</td>
</tr>
<tr>
<td>Rare:</td>
<td>Taste disturbance</td>
</tr>
<tr>
<td>SOC/frequency</td>
<td>Adverse reaction</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Blurred vision</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting</td>
</tr>
<tr>
<td>Rare:</td>
<td>Dry mouth, stomatitis, gastrointestinal candidiasis</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Increased liver enzymes</td>
</tr>
<tr>
<td>Rare:</td>
<td>Hepatitis with or without jaundice</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Hepatic failure, encephalopathy in patients with pre-existing liver disease</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Dermatitis, pruritus, rash, urticaria</td>
</tr>
<tr>
<td>Rare:</td>
<td>Alopecia, photosensitivity</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Muscular weakness</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare:</td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Malaise, peripheral oedema</td>
</tr>
<tr>
<td>Rare:</td>
<td>Increased sweating</td>
</tr>
</tbody>
</table>

4.9 **Overdose**

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC01

Mechanism of action

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once-daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme
H+ K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides for rapid and sustained inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

Other effects related to acid inhibition
During long-term treatment gastric glandular cysts have been reported in 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 acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

5.2 Pharmacokinetic properties

Absorption
Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution
The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight.
Omeprazole is 97% plasma protein bound.

Metabolism
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole
is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg
omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a
functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also
higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

**Excretion**
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and
repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with
no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of
omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating
from bile secretion.

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and
results in a non-linear dose-AUC relationship 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 omeprazole and/or its metabolites (e.g. the sulphone).
No metabolite has been found to have any effect on gastric acid secretion.

**Special populations**

**Impaired hepatic function**
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased
AUC. Omeprazole has not shown any tendency to accumulate with once-daily dosing.

**Impaired renal function**
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are
unchanged in patients with reduced renal function.

**Elderly**
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

5.3 **Preclinical safety data**
Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated
with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid
inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump
inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any
individual active substance.

6 **PHARMACEUTICAL PARTICULARS**
6.1 **List of excipients**
**Capsules content:**
- Low-substituted hydroxypropyl cellulose
- Microcrystalline cellulose
- Lactose anhydrous
- Croscarmellose sodium
- Povidone (K 25)
- Polysorbate 80
- Hypromellose phthalate
- Dibutyl sebacate
- Talc

**Capsule shell:**
- Carrageenan
- Potassium chloride
- Titanium dioxide E171
- Yellow iron oxide E172
- Red iron oxide E172
- Hypromellose
Printing ink:
Shellac
Propylene glycol
Ammonium hydroxide
Potassium hydroxide
Black iron oxide E172

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original package, in order to protect from light and moisture.
Keep the tablet container tightly closed.

6.5 Nature and contents of container
Aluminum/Aluminium blister

White HDPE tablet container with PP screw cap with Child resistant closure or Tamper evident closure.

The screw cap contains a capsule with desiccant.

Pack sizes:
Blister: 7, 14 and 28 gastro-resistant capsules, hard
Tablet container: 7, 10, 14, 15, 20 and 28 gastro-resistant capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Sandoz Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/1224

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2012

10 DATE OF REVISION OF THE TEXT
02/03/2012
1 NAME OF THE MEDICINAL PRODUCT
Omeprazole 20 mg Gastro-resistant Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant capsule, hard contains 20 mg of omeprazole.

Excipient(s):
Each 20 mg gastro-resistant capsule, hard contains 117 mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant capsule, hard (Gastro-resistant capsule)
White cap, white body, each imprinted with “OME 20” containing dull yellowish, brown granules

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Omeprazole 20 mg Gastro-resistant Capsules are indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

4.2 Posology and method of administration

Posology in adults
The recommended dose is 20 mg once daily for 14 days.
It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms.
The majority of patients achieve complete relief of heartburn within 7 days. Once complete relief of symptoms has occurred, treatment should be discontinued.

Special populations

Impaired renal function
Dose adjustment is not needed in patients with impaired renal function (see section 5.2).

Impaired hepatic function
Patients with impaired hepatic function should be advised by a doctor before taking Omeprazole 20 mg Gastro-resistant Capsules (see section 5.2).

Elderly (> 65 years old)
Dose adjustment is not needed in the elderly (see section 5.2).

Paediatric population
This medicinal product should not be used in children and adolescents under the age of 18 years.

Method of administration
It is recommended to take Omeprazole 20 mg Gastro-resistant Capsules in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

For patients with swallowing difficulties
Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water. Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

4.3 Contraindications
Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients.

Omeprazole like other proton pump inhibitors must 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, haematemeses or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

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

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, 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 omeprazole and clopidogrel should be discouraged.

Omeprazole 20 mg Gastro-resistant Capsules contain lactose. Therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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).

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any ‘over-the-counter’ (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should be instructed to consult a doctor if:

- They have had previous gastric ulcer or gastrointestinal surgery
- They are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients should not take omeprazole as a preventative medication.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

*Nelfinavir, atazanavir*

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75-90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. 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 to atazanavir 300 mg/ritonavir 100 mg once daily.
Digoxin
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

Clopidogrel
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.

Other active substances
The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism
Saquinavir
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Effects of other active substances on the pharmacokinetics of omeprazole
Inhibitors of CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole’s rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John’s wort) may lead to decreased omeprazole serum levels by increasing omeprazole’s rate of metabolism.
4.6 **Fertility, Pregnancy and lactation**

**Pregnancy**
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

**Lactation**
Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

**Fertility**
There are no data on the effect of omeprazole on human fertility. Fertility was unaffected following omeprazole treatment in animal studies.

4.7 **Effects on ability to drive and use machines**

Omeprazole 20 mg Gastro-resistant Capsules is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 **Undesirable effects**

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common \((\geq 1/10)\), Common \((\geq 1/100 \text{ to } < 1/10)\), Uncommon \((\geq 1/1,000 \text{ to } < 1/100)\), Rare \((\geq 1/10,000 \text{ to } < 1/1,000)\), Very rare \((< 1/10,000)\), Not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>SOC/frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Agranulocytosis, pancytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Hypomagnesaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Rare:</td>
<td>Agitation, confusion, depression</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Aggression, hallucinations</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Headache</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Dizziness, paraesthesia, somnolence</td>
</tr>
<tr>
<td>Rare:</td>
<td>Taste disturbance</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>
### SOC/frequency vs. Adverse reaction

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Rare: Dry mouth, stomatitis, gastrointestinal candidiasis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: Increased liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Rare: Hepatitis with or without jaundice</td>
<td></td>
</tr>
<tr>
<td>Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: Dermatitis, pruritus, rash, urticaria</td>
<td></td>
</tr>
<tr>
<td>Rare: Alopecia, photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Arthralgia, myalgia</td>
<td></td>
</tr>
<tr>
<td>Very rare: Muscular weakness</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Interstitial nephritis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare: Gynaecomastia</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: Malaise, peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Rare: Increased sweating</td>
<td></td>
</tr>
</tbody>
</table>

### 4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC01

**Mechanism of action**

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once-daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H⁺ K⁺-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

**Pharmacodynamic effects**

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.
Effect on gastric acid secretion

Oral dosing with omeprazole once daily provides for rapid and sustained inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

Other effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in 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 acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

5.2 Pharmacokinetic properties

Absorption

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.
Excretion
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship 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 omeprazole and/or its metabolites (e.g. the sulphone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations

Impaired hepatic function
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once-daily dosing.

Impaired renal function
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

5.3 Preclinical safety data
Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsules content:
Low-substituted hydroxypropyl cellulose
Microcrystalline cellulose
Lactose anhydrous
Croscarmellose sodium
Povidone (K 25)
Polysorbate 80
Hyromellose phthalate
Dibutyl sebacate
Talc

Capsule shell:
Carrageenan
Potassium chloride
Titanium dioxide E171
Hyromellose

Printing ink:
Shellac
Propylene glycol
Ammonium hydroxide
Potassium hydroxide
Black iron oxide E172

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original package, in order to protect from light and moisture.
Keep the tablet container tightly closed.

6.5 Nature and contents of container
Aluminum/Aluminium blister

White HDPE tablet container with PP screw cap with Child resistant closure or Tamper evident closure.

The screw cap contains a capsule with desiccant.

Pack sizes:
Blister: 7 and 14 gastro-resistant capsules, hard
Tablet container: 7, 10 and 14 gastro-resistant capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Sandoz Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/1225

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2012

10 DATE OF REVISION OF THE TEXT
02/03/2012
Omeprazole 10 mg and 20 mg Gastro-resistant Capsules

Package Leaflet Information for the User

Omeprazole 10 mg Gastro-resistant Capsules

Omeprazole contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors' which work by reducing the amount of acid that your stomach produces.

Omeprazole is used mainly to treat the short-term treatment of reflux symptoms (for example, heartburn and indigestion).

It may also be used to prevent the recurrence of ulcers in the oesophagus, stomach and duodenum. This may be in patients who have had surgery to the oesophagus.

How to take Omeprazole

1. What Omeprazole is and what it is used for

Omeprazole contains the active substance omeprazole. It belongs to a group of medicines called 'proton pump inhibitors', which work by reducing the amount of acid that your stomach produces.

Omeprazole is used mainly to treat the short-term treatment of reflux symptoms (for example, heartburn and indigestion). It may also be used to prevent the recurrence of ulcers in the oesophagus, stomach and duodenum. This may be in patients who have had surgery to the oesophagus.

2. Before you take Omeprazole

Do not take Omeprazole if:

- you are allergic to omeprazole or any of the other ingredients of Omeprazole 10 mg Gastro-resistant Capsules;
- you are allergic to medicines containing other proton pump inhibitors, such as lansoprazole, rabeprazole, pantoprazole, famotidine, ranitidine, or cimetidine;
- you are taking a medicine containing rifampicin (for example, rifampicin, rifabutin, etc.);
- you are not sure if you have had your doctor or pharmacist before taking Omeprazole.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- other proton pump inhibitors (such as lansoprazole)
- other medicines used to treat heartburn (such as ranitidine)
- other medicines used to treat ulcers (such as enemias)
- other medicines used to treat peptic ulcer disease (such as famotidine)
- other medicines used to treat infection (such as clarithromycin, tetracyclines, rifampicin, rifabutin).

Tell your doctor or pharmacist if you are taking any of the following medicines:

- antacids
- other medicines used to treat heartburn
- other medicines used to treat ulcers
- other medicines used to treat peptic ulcer disease
- other medicines used to treat infection.

3. How to take Omeprazole

Always take Omeprazole exactly as described in the leaflet. You should take it by mouth. The usual adult dose is 1 capsule daily. The usual daily dose is 2 capsules daily. This dose should be taken in the evening, 1 hour before you eat your main meal.

Never exceed the daily dose of 2 capsules.

Keep the leaflet and any remaining capsules to show your doctor or pharmacist when you next see them.

Tell your doctor or pharmacist if you are taking any other medicines, even those bought without prescription. This includes medicines sold in supermarkets and herbal remedies.

4. Possible side effects

In addition to a few patients having minor side effects, mainly headache and nausea, no other side effects have been reported.

5. How to store Omeprazole

Keep the leaflet and any remaining capsules to show your doctor or pharmacist when you next see them.

Tell your doctor or pharmacist if you are taking any other medicines, even those bought without prescription. This includes medicines sold in supermarkets and herbal remedies.
Omeprazole 10 mg and 20 mg Gastro-resistant Capsules

UK/H/4500/001-2/DC

- To make sure that you have read all of the information, close the package and look at each label and leaflet before you start taking the medicine.
- Do not close or open the package.
- Close the package and look at each label and leaflet before you start taking the medicine.
- Do not take Omeprazole if you are allergic or sensitive to any of the ingredients, unless your doctor or pharmacist tells you that it is safe to do so.
- If you take Omeprazole, you should:
  - Follow the instructions on the label and leaflet carefully.
  - Use Omeprazole exactly as instructed by your doctor or pharmacist.
  - Keep Omeprazole out of reach of children.
  - Do not share Omeprazole with anyone else, even if they have the same condition as you.

4 Possible side effects

Like all medicines, Omeprazole can cause side effects, although not everyone gets them. Some possible side effects are:

- Headache.
- Nausea.
- Vomiting.
- Loss of appetite.
- Stomach pain.
- Chest pain.
- Diarrhoea.
- Sleep disorders.
- Increased sweating.
- Muscle weakness.
- Dizziness in men.
- Hypersensitivity.

Omeprazole may very rarely cause allergic reactions.

If you experience any other side effects, please consult your doctor or pharmacist.

5 How to store Omeprazole

Keep Omeprazole and all other medicines out of the reach of children. Store in a cool, dry place.

Do not store Omeprazole in the bathroom where it may get damp. Keep it out of the reach of children.

Most Omeprazole 10 mg Gastro-resistant Capsules contain:

- Omeprazole 10 mg.
- Dicalcium phosphate (SUSP).
- Magnesium stearate (SUSP).
- Sodium lauryl sulphate (SUSP).
- Hydroxypropyl methylcellulose (SUSP).
- Talc (SUSP).
- Shellac (SUSP).
- Calamine (SUSP).
- Magnesium hydroxide (SUSP).
- Talc (SUSP).

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  - Follow the instructions on the label and leaflet carefully.
  - Use Omeprazole exactly as instructed by your doctor or pharmacist.
  - Keep Omeprazole out of reach of children.
  - Do not share Omeprazole with anyone else, even if they have the same condition as you.

4 Possible side effects

Like all medicines, Omeprazole can cause side effects, although not everyone gets them. Some possible side effects are:

- Headache.
- Nausea.
- Vomiting.
- Loss of appetite.
- Stomach pain.
- Chest pain.
- Diarrhoea.
- Sleep disorders.
- Increased sweating.
- Muscle weakness.
- Dizziness in men.
- Hypersensitivity.

Omeprazole may very rarely cause allergic reactions.

If you experience any other side effects, please consult your doctor or pharmacist.

5 How to store Omeprazole

Keep Omeprazole and all other medicines out of the reach of children. Store in a cool, dry place.

Do not store Omeprazole in the bathroom where it may get damp. Keep it out of the reach of children.

Most Omeprazole 10 mg Gastro-resistant Capsules contain:

- Omeprazole 10 mg.
- Dicalcium phosphate (SUSP).
- Magnesium stearate (SUSP).
- Sodium lauryl sulphate (SUSP).
- Hydroxypropyl methylcellulose (SUSP).
- Talc (SUSP).
- Shellac (SUSP).
- Calamine (SUSP).
- Magnesium hydroxide (SUSP).
- Talc (SUSP).

- Do not take Omeprazole if you are allergic or sensitive to any of the ingredients, unless your doctor or pharmacist tells you that it is safe to do so.
- If you take Omeprazole, you should:
  - Follow the instructions on the label and leaflet carefully.
  - Use Omeprazole exactly as instructed by your doctor or pharmacist.
  - Keep Omeprazole out of reach of children.
  - Do not share Omeprazole with anyone else, even if they have the same condition as you.

4 Possible side effects

Like all medicines, Omeprazole can cause side effects, although not everyone gets them. Some possible side effects are:

- Headache.
- Nausea.
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- Dizziness in men.
- Hypersensitivity.

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- Dicalcium phosphate (SUSP).
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- Sodium lauryl sulphate (SUSP).
- Hydroxypropyl methylcellulose (SUSP).
- Talc (SUSP).
- Shellac (SUSP).
- Calamine (SUSP).
- Magnesium hydroxide (SUSP).
- Talc (SUSP).
The below text was approved for Omeprazole 20 mg Gastro-resistant Capsules (PL 04416/1225; UK/H/4500/002/DC at the end of the decentralised procedure. The Marketing Authorisation Holder is required to submit the leaflet mock-up to the relevant regulatory authorities before marketing any pack size in a particular member state.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Omeprazole 20 mg Gastro-resistant Capsules

Omeprazole

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to take Omeprazole Capsules carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 14 days.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

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

1. WHAT OMEPRAZOLE IS AND WHAT IT IS USED FOR

Omeprazole contain the active substance omeprazole. It belongs to a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces.

Omeprazole is used in adults for the short-term treatment of reflux symptoms (for example, heartburn, acid regurgitation).

Reflux is the backflow of acid from the stomach into the gullet “foodpipe”, which may become inflamed and painful. This may cause you symptoms such as a painful burning sensation in the chest rising up to the throat (heartburn) and a sour taste in the mouth (acid regurgitation).

It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms.

2. BEFORE YOU TAKE OMEPRAZOLE

Do not take Omeprazole
- if you are allergic (hypersensitive) to omeprazole or any of the other ingredients of Omeprazole 20 mg Gastro-resistant Capsules.
- if you are allergic to medicines containing other proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole, esomeprazole).
- if you are taking a medicine containing rifamycin (for HIV infection).

If you are not sure, talk to your doctor or pharmacist before taking Omeprazole.

Take special care with Omeprazole
Do not take Omeprazole for more than 14 days without consulting a doctor. If you do not experience relief, or if you experience a worsening of symptoms, consult your doctor.

Omeprazole may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Omeprazole or while you are taking it, talk to your doctor straight away:
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
• You pass black stools (blood-stained faeces).
• You experience severe or persistent diarrhoea, as omeprazole has been associated with a small increase in infectious diarrhoea.
• You have had previous gastric ulcer or gastrointestinal surgery.
• You are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
• You continuously suffer from indigestion or heartburn for 4 or more weeks.
• You have jaundice or severe liver disease.
• You are aged over 55 years with new or recently changed symptoms.

Patients should not take omeprazole as a preventative medication.

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 Omeprazole can affect the way some medicines work and some medicines can have an effect on Omeprazole 20 mg Gastro-resistant Capsules.

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

You should specifically tell your doctor or pharmacist if you are taking clopidogrel (used to prevent blood clots (thrombi)).

Tell your doctor or pharmacist if you are taking any of the following medicines:
• Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
• Digoxin (used to treat heart problems).
• 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 Omeprazole.
• Medicines that are used to thin your blood, such as warfarin or other vitamin K blockers. Your doctor may need to monitor you when you start or stop taking Omeprazole.
• Rifampicin (used to treat tuberculosis).
• Atazanavir (used to treat HIV infection).
• Tacroliumus (in cases of organ transplantation).
• St John’s wort (Hypericum perforatum) (used to treat mild depression).
• Cilostazol (used to treat intermittent claudication).
• Saquinavir (used to treat HIV infection).

Taking Omeprazole with food and drink
You can take your capsules with food or on an empty stomach.

Pregnancy and breastfeeding
Before taking Omeprazole, tell your doctor or pharmacist if you are pregnant or trying to get pregnant. Your doctor will decide whether you can take Omeprazole during this time.

Your doctor will decide whether you can take Omeprazole if you are breastfeeding.

Driving and using machines
Omeprazole is not likely to affect your ability to drive or use any tools or machines. Side effects such as dizziness and visual disturbances may occur (see section 4). If affected, you should not drive or operate machinery.

Important information about some of the ingredients of Omeprazole
Omeprazole contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
3. HOW TO TAKE OMEPRAZOLE

Always take Omeprazole exactly as described in this leaflet. You should check with your doctor or pharmacist if you are not sure.
The usual dose is one 20 mg capsule or two 10 mg capsules once a day for 14 days. Contact your doctor if you are not free from symptoms after this period.
It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms.

Taking this medicine
• It is recommended that you take your capsules in the morning.
• You can take your capsules with food or on an empty stomach.
• Swallow your capsules whole with half a glass of water. Do not chew or crush the capsules. This is because the capsules 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 capsules
• If you have trouble swallowing the capsules:
  - Open the capsule and swallow the contents directly with half a glass of water or put the contents into a glass of still (non-fizzy) water, any acidic fruit juice (e.g. apple, orange or pineapple) or apple sauce.
  - Always stir the mixture just before drinking it (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes.
  - 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. Do not use milk or fizzy water. The solid pieces contain the medicine - do not chew or crush them.

Children
This medicine should not be used in children and adolescents under the age of 18 years.

If you take more Omeprazole than you should
If you take more Omeprazole than recommended, talk to your doctor or pharmacist straight away.

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

4. POSSIBLE SIDE EFFECTS

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

If you notice any of the following rare but serious side effects, stop taking Omeprazole 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.

Side effects may occur with certain frequencies, which are defined as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>Common:</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare:</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
</tbody>
</table>
Omeprazole 10 mg and 20 mg Gastro-resistant Capsules

| Very rare: | affects less than 1 user in 10,000 |
| Not known: | frequency cannot be estimated from the available data |

Other side effects include:

**Common side effects**
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

**Uncommon side effects**
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as “pins and needles”, feeling sleepy.
- Spinning feeling (vertigo).
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (fevers) and itchy skin.
- Generally feeling unwell and lacking energy.

**Rare side effects**
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Allergic reactions, sometimes very severe, including swelling of the lips, tongue and throat, fever, wheezing.
- 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).
- Dry mouth.
- An inflammation of the inside of 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 pains (arthritis) or muscle pains (myalgia).
- Severe kidney problems (interstitial nephritis).
- Increased sweating.

**Very rare side effects**
- 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 pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Enlarged breasts in men.
- Hypomagnesaemia.

Omeprazole 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 medicine 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 OMEPRAZOLE

Keep out of the reach and sight of children.

Do not use Omeprazole after the expiry date which is stated on the blister and outer carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

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

Keep the tablet container tightly closed

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

6. FURTHER INFORMATION

What Omeprazole 20 mg Gastro-resistant Capsules contains

The active substance is omeprazole.

Each gastro-resistant capsule, hard contains 20mg of omeprazole.

The other ingredients are:

- **Capsule content:**
  - low-substituted hydroxypropyl cellulose, microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, Povidone (K 25), Polysorbate 80, hypromellose phthalate, dibutyl sebacate, talc.

- **Capsule shell:**
  - Carrageenan, potassium chloride, titanium dioxide (E171), hypromellose.

- **Printing ink:**
  - Shellac, propylene glycol, ammonium hydroxide, potassium hydroxide, black iron oxide (E172).

What Omeprazole 20 mg Gastro-resistant Capsules looks like and contents of the pack

White cap, white body, each imprinted with “OME 20” containing dull yellowish, brown granules.

Pack sizes:

- Blister: 7 and 14 gastro-resistant capsules, hard
- White plastic tablet container with screw cap: 7, 10 and 14 gastro-resistant capsules, hard

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

**Marketing Authorisation Holder**

Sandoz Limited
Finley Business Park
Finley
Omeprazole 10 mg and 20 mg Gastro-resistant Capsules

Camberley
Surrey
GU14 7SR
United Kingdom

Manufacturer
Lek Pharmaceuticals d.d.
Verovškova 67,
1523 Ljubljana
Slovenia

LEK S.A.
ul. Domaniewska 50 C.
02-572 Warszawa
Poland

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Bielefeld
Germany

Salutas Pharma GmbH
Diezelstrasse 5
70839 Geringen
Germany

This leaflet was last approved in 02/2012 (to be amended after approval)
Omeprazole 10 mg and 20 mg Gastro-resistant Capsules

SANDOZ

Omeprazole 10 mg Gastro-resistant Capsules
SZX0005FL000
PL 04416/1124
Sandoz Ltd

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PL 04416/1124
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SZX0005FL000
PL 04416/1124
Sandoz Ltd
The below text was approved for Omeprazole 20 mg Gastro-resistant Capsules (PL 04416/1225; UK/H/4500/002/DC at the end of the decentralised procedure. The Marketing Authorisation Holder is required to submit mock-ups of the labelling to the relevant regulatory authorities before marketing any pack size in a particular member state.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

Carton box for blister(s)

1. **NAME OF THE MEDICINAL PRODUCT**

Omeprazole 20 mg Gastro-resistant Capsules
Omeprazole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each gastro resistant capsule, hard contains 20 mg of omeprazole.

3. **LIST OF EXCIPIENTS**

Contains Lactose

See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

Gastro resistant capsule, hard.

- 7 gastro resistant capsule, hard
- 14 gastro resistant capsule, hard

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Swallow the capsules whole.

Read the package leaflet before use.
Oral 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:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

Sandoz Limited
Farnley Business Park
Farnley
Camberley
Surrey
GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 04416/1225

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omeprazole 20 mg Gastro-resistant Capsules
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
</tr>
</tbody>
</table>

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Omeprazole 20 mg Gastro-resistant Capsules
Omeprazole

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Sandoz Limited

3. **EXPIRY DATE**

EXP.

4. **BATCH NUMBER**

Lot.

5. **OTHER**

PL 04416/1225
1. **NAME OF THE MEDICINAL PRODUCT**

Omeprazole 20 mg Gastro-resistant Capsules
Omeprazole

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each gastro resistant capsule, hard contains 20 mg of omeprazole.

3. **LIST OF EXCIPIENTS**

Contains Lactose

See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

Gastro resistant capsule, hard

7 gastro resistant capsule, hard
10 gastro resistant capsule, hard
14 gastro resistant capsule, hard

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Swallow the capsules whole.

Read the package leaflet before use.
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7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

Keep the tablet container tightly closed.

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

Sandoz Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 04416/1225

13. MANUFACTURER'S BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omeprazole 20 mg Gastro-resistant Capsules
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Label for HDPE tablet container

1. NAME OF THE MEDICINAL PRODUCT

Omeprazole 20 mg Gastro-resistant Capsules
Omeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro resistant capsule, hard contains 20 mg of omeprazole.

3. LIST OF EXCIPIENTS

Contains Lactose

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Gastro resistant capsule, hard

7 gastro resistant capsule, hard
10 gastro resistant capsule, hard
14 gastro resistant capsule, hard

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Swallow the capsules whole.

Read the package leaflet before use.

Oral use.

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Keep out of the reach and sight of children.
7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP:

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 30°C.

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

   Keep the tablet container tightly closed.

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**

    Sandoz Limited
    Friemley Business Park
    Friemley
    Camberley
    Surrey
    GU16 7SR
    United Kingdom

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

    PL 04416/1225

13. **MANUFACTURER'S BATCH NUMBER**

    Lot.

14. **GENERAL CLASSIFICATION FOR SUPPLY**

    POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

    Omeprazole 20 mg Gastro-resistant Capsules
Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Omeprazole 10 mg and 20 mg Gastro-resistant Capsules (PL 04416/124-5; UK/H/4500/001-2/DC) could be approved. Omeprazole 10 mg Gastro-resistant Capsules is a pharmacy (P) medicine and Omeprazole 20 mg Gastro-resistant Capsules is a prescription-only medicine (POM). These medicinal products are indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium, Bulgaria, Estonia, France, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Poland, Portugal, Romania and Slovak Republic as Concerned Member States (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal product for these applications is Losec 20 mg Capsules (AstraZeneca UK Limited, UK), which was first granted in the UK on 09 May 1989. Reference is also made to the corresponding 10 mg strength UK reference product Losec 10 mg Capsules (AstraZeneca UK Limited, UK), which was first authorised in the UK on 06 January 1994.

The active ingredient, omeprazole is a specific inhibitor of the gastric H+, K+-ATPase enzyme (the proton pump) that is responsible for acid secretion by the parietal cells of the stomach.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

Three (two single-dose and one multiple-dose) bioequivalence studies were submitted to support these applications, comparing the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) versus the reference product Losec 20 mg Capsules (AstraZeneca UK Limited, UK), and the test product Ortanol 40 mg (manufactured by Lek Pharmaceuticals d.d, Slovenia) versus the reference product Losec 40 mg Capsules (AstraZeneca UK Limited, UK). During product development, Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) was the name used for the Omeprazole 20 mg Gastro-resistant Capsules (Sandoz Limited, UK). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing 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, 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 and CMS considered that the applications could be approved at the end of procedure (Day 210) on 02 February 2011. After a subsequent national phase, licences were granted in the UK on 02 March 2012.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/4500/001/DC: Omeprazole 10 mg Gastro-resistant Capsules  
| Name(s) of the active substance (INN) | Omeprazole  
| Pharmacotherapeutic classification (ATC code) | Proton pump inhibitors (ATC code: A02BC01)  
| Pharmaceutical form and strength(s) | Gastro-resistant capsule, hard  
10 mg and 20 mg  
| Reference numbers for the Decentralised Procedure | UK/H/4500/001-2/DC  
| Reference Member State (RMS) | United Kingdom  
| Concerned Member States (CMS) | Belgium, Bulgaria, Estonia, France, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Poland, Portugal, Romania and Slovak Republic  
| Marketing Authorisation Number(s) | PL 04416/1224-5  
| Name and address of the authorisation holder | Sandoz Limited  
Frimley Business Park, Frimley  
Camberley  
Surrey GU16 7SR  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Omeprazole
Chemical Name: 5 - Methoxy-2-[(RS)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazole
Molecular formula: C_{17}H_{19}N_{3}O_{3}S
Structure:

![Structure of Omeprazole]

Molecular mass: 345.4 g/mol
Appearance: A white or almost white powder, very slightly soluble in water, soluble in methylene chloride, sparingly soluble in alcohol and methanol. Dissolves in dilute solutions of alkali hydroxides.

Omeprazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance omeprazole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability for each active substance manufacturer.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the capsule core, capsule shell and printing ink, namely low-substituted hydroxypropyl cellulose, microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, povidone (K 25), Polysorbate 80, hypromellose phthalate, dibutyl sebacate, tcalc, carrageenan, potassium chloride, titanium dioxide (E171), yellow iron oxide (E172) (10 mg strength capsule only), red iron oxide (E172) (10 mg strength capsule only), black iron oxide (E172), shellac, propylene glycol, ammonium hydroxide and potassium hydroxide. Appropriate justification for the inclusion of each excipient has been provided.

With the exception of low-substituted hydroxypropyl cellulose, dibutyl sebacate, yellow iron oxide(E172), red iron oxide (E172), black iron oxide (E172), shellac, propylene glycol, ammonium hydroxide and potassium hydroxide, all excipients comply with their respective European Pharmacopoeia monograph. Low-substituted hydroxypropyl cellulose, dibutyl sebacate, shellac, yellow iron oxide E172, red iron oxide E172, black iron oxide E172, ammonium hydroxide and potassium hydroxide, are controlled to National Formulary specifications. In addition, the specifications for yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172) are in compliance with current EU Directives concerning the use of colouring agents. Propylene glycol is controlled to its United States Pharmacopoeial specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose anhydrous, none of the excipients contain materials of animal or human origin. The supplier of lactose anhydrous has confirmed that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions.
as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose anhydrous.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Losec 10 mg and 20 mg Capsules (AstraZeneca UK Limited, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

Both strengths of the capsules are packaged in either:

1. aluminium/aluminium blisters in pack sizes of 7 and 14 and gastro-resistant capsules, hard. In addition, the 10 mg strength capsule is available in a pack size of 28 gastro-resistant capsules.
2. white high-density polyethylene (HDPE) tablet containers with polypropylene (PP) screw caps containing capsules with desiccant, with child-resistant closures or tamper-evident closures in pack sizes of 7, 10 and 14 gastro-resistant capsules, hard. In addition, the 10 mg strength capsule is available in pack sizes of 15, 20 and 28 gastro-resistant capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been proposed, with the storage conditions ‘Do not store above 30°C. Store in the original package, in order to protect from light and moisture.’ and ‘Keep the tablet container tightly closed’ (for the HDPE container only).
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are satisfactory from a pharmaceutical perspective. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) Forms
All aspects of the MAA forms are pharmaceutically satisfactory.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS
The clinical pharmacology of omeprazole is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence studies:

Study 1
A randomised, open label, single-dose, semi-replicate, three-period, crossover study comparing the pharmacokinetics of the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d., Slovenia) and the reference product Mopral 20 mg Capsules (AstraZeneca Limited, UK) in healthy, non-smoking, adult male subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. The subjects were randomised to receive single doses of either the test product (A) or the reference product (B) on two occasions, according to the sequence ABB or BAA. Blood samples were collected before and up to and including 15 hours after each administration. The washout period between the treatment periods was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (least square means, ratios and confidence intervals [CI]) of omeprazole</th>
<th>Omeprazole 20 mg (Test)</th>
<th>Losec 20 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-t}$ (ng h/mL)</td>
<td>336.714</td>
<td>357.876</td>
<td>94.1</td>
<td>87.8–100.8</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng h/mL)</td>
<td>341.654</td>
<td>359.295</td>
<td>95.1</td>
<td>88.8–101.8</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>211.702</td>
<td>228.054</td>
<td>92.8</td>
<td>82.6–104.3</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ 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

$C_{\text{max}}$ maximum plasma concentration

Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio of geometric means for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ lie within the acceptable limits of 80% to 125%, in line with the ‘Note for Guidance on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d., Slovenia) is bioequivalent to the reference product Mopral 20 mg Capsules (AstraZeneca UK Limited, UK) under fasting conditions.

Study 2
A randomised, open label, single-dose, semi-replicate, three-period, crossover study comparing the pharmacokinetics of the test product Omeprazole 20 mg Delay-Release Capsules (manufactured by Lek Pharmaceuticals d.d., Slovenia) and the reference product Mopral 20 mg capsules (AstraZeneca Limited, UK) in healthy, non-smoking, adult male subjects under fed conditions.

The subjects were given a single dose of either treatment with 240 ml of water, 30 minutes after administration of a standard high fat breakfast. The subjects were randomised to receive a single dose of either the test product (A) or the reference product (B) on two occasions, according to the sequence ABB or BAA. Blood samples were collected before and up to 24
hours after each administration. The washout period between the treatment periods was 7 days. The pharmacokinetic results are presented below:

### Study 2
A randomised, open label, multiple-dose, two-sequence, two-way, crossover study comparing the pharmacokinetics of the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) and the reference product Losec 20 mg capsules (AstraZeneca UK Limited, UK) in healthy, non-smoking, adult male subjects under fasting conditions.

The subjects were given 20 mg of either treatment with 240 ml of water after an overnight fast, every 24 hours for 8 days. Capsules were swallowed whole. Blood samples were collected before administration on Days 1, 6, 7 and before and up to 24 hours after administration on Day 8. The washout period between the treatment periods was 14 days. The pharmacokinetic results are presented below:

### Pharmacokinetic parameters (least square means, ratios and confidence intervals [CI]) of omeprazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Omeprazole 20 mg (Test)</th>
<th>Losec 20 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-t}) (pg.hr/mL)</td>
<td>318.24</td>
<td>341.58</td>
<td>93.2</td>
<td>86.6–100.2</td>
</tr>
<tr>
<td>AUC(_{0-inf}) (pg.hr/mL)</td>
<td>356.2</td>
<td>381.8</td>
<td>93.3</td>
<td>86.2–101.0</td>
</tr>
<tr>
<td>C(_{max}) (pg/mL)</td>
<td>134.376</td>
<td>128.137</td>
<td>104.9</td>
<td>92.5–118.9</td>
</tr>
</tbody>
</table>

AUC\(_{0-inf}\) area under the plasma concentration-time curve from time zero to infinity
AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to t hours
C\(_{max}\) maximum plasma concentration
Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio of geometric means for AUC\(_{0-t}\), AUC\(_{0-inf}\) and C\(_{max}\) lie within the acceptable limits of 80% to 125%, in line with the ‘Note for Guidance on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) is bioequivalent to the reference product Mopral 20 mg Capsules (AstraZeneca UK Limited, UK) under fed conditions.

### Study 3
A randomised, open label, multiple-dose, two-sequence, two-way, crossover study comparing the pharmacokinetics of the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) and the reference product Losec 20 mg capsules (AstraZeneca UK Limited, UK) in healthy, non-smoking, adult male subjects under fasting conditions.

The subjects were given 20 mg of either treatment with 240 ml of water after an overnight fast, every 24 hours for 8 days. Capsules were swallowed whole. Blood samples were collected before administration on Days 1, 6, 7 and before and up to 24 hours after administration on Day 8. The washout period between the treatment periods was 14 days. The pharmacokinetic results are presented below:

### Pharmacokinetic parameters (least square means, ratios and confidence intervals [CI]) of omeprazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Omeprazole 20 mg (Test)</th>
<th>Losec 20 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{τ(ss)}) (h*ng/mL)</td>
<td>877.87</td>
<td>888.75</td>
<td>99</td>
<td>95–103</td>
</tr>
<tr>
<td>C(_{max(ss)}) (pg/mL)</td>
<td>481.68</td>
<td>490.69</td>
<td>98</td>
<td>92–105</td>
</tr>
</tbody>
</table>

AUC\(_{τ(ss)}\) area under the plasma concentration-time curve over the final dosing interval
C\(_{max(ss)}\) maximum plasma concentration over the final dosing interval
Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio of geometric means for AUC\(_{0-t}\), AUC\(_{0-inf}\) and C\(_{max}\) lie within the acceptable limits of 80% to 125%, in line with the ‘Note for Guidance on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Omeprazole 20 mg Delayed-Release Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) is bioequivalent to the reference product Mopral 20 mg Capsules (AstraZeneca UK Limited, UK) at steady state under fasting conditions.
Study 4
A randomised, open label, multiple-dose, two-sequence, two-way, crossover study comparing the pharmacokinetics of the test product Ortanal (omeprazole) 40 mg capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) and the reference product Losec 40 mg capsules (AstraZeneca UK Limited, UK) in healthy, non-smoking, adult male subjects under fasting conditions.

The subjects were given 40 mg of either treatment with 240 ml of water after an overnight fast, every 24 hours for 8 days. Capsules were swallowed whole. Blood samples were collected before administration on Days 1, 6, 7 and before and up to 24 hours after administration on Day 8. The washout period between the treatment periods was 14 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Ortanal 40 mg (Test)</th>
<th>Losec 40 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;τ&lt;/sub&gt;</strong>&lt;sup&gt;ss&lt;/sup&gt; (h*ng/mL)</td>
<td>3359.58</td>
<td>3414.22</td>
<td>98</td>
<td>95–102</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong>&lt;sup&gt;ss&lt;/sup&gt; (ng/mL)</td>
<td>1230.30</td>
<td>1325.21</td>
<td>93</td>
<td>87–99</td>
</tr>
</tbody>
</table>

AUC<sub>τ</sub> area under the plasma concentration-time curve over the final dosing interval
C<sub>max</sub> maximum plasma concentration over the final dosing interval

Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio of geometric means for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> lie within the acceptable limits of 80% to 125%, in line with the ‘Note for Guidance on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Ortanal (omeprazole) 40 mg Capsules (manufactured by Lek Pharmaceuticals d.d, Slovenia) is bioequivalent to the reference product Mopral 20 mg Capsules (AstraZeneca UK Limited, UK) at steady state under fasting conditions.

Overall conclusion
Based on the submitted bioequivalence studies, Omeprazole 20 mg Gastro-resistant Capsules (Sandoz Limited, UK) are considered bioequivalent with the reference product Losec 20 mg Capsules (AstraZeneca UK Limited, UK).

As the 10 mg and 20mg strengths of the product meet all the criteria specified in the Guideline on the Investigation of Bioequivalence for a bio waiver (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence studies with the 20 mg capsule strength can be extrapolated to the 10 mg capsule strength.

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

Safety
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence studies.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person.
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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PILs) AND LABELLING**
The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**CONCLUSION**
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Omeprazole 10 mg and 20 mg Gastro-resistant Capsules 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. As the pharmacokinetics, pharmacodynamics and toxicology of omeprazole are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 10 mg strength capsule and the reference product Losec 20 mg Capsules (AstraZeneca UK Limited). As the 10 mg and 20 mg strengths of the product meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence studies with the 20 mg capsule strength can be extrapolated to the 10 mg capsule strength.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of omeprazole is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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