Public Assessment Report

Mutual Recognition Procedure

Omeprazole 10 mg Capsules
Omeprazole 20 mg Capsules
Omeprazole 40 mg Capsules

UK/H/799/01-03
UK licence no: PL 04416/0651-3

Sandoz Limited

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Module 1

Product Name	Omeprazole 10mg Capsules Omeprazole 20mg Capsules Omeprazole 40mg Capsules
Type of Application	Generic, Article 10.1
Active Substance	Omeprazole
Form	Capsules
Strength	10mg, 20mg, 40mg
MA Holder	Sandoz Limited, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE
RMS	UK
CMS	Austria, Belgium, Czech Republic, Estonia, Germany, Greece, Hungary, Lithuania, Luxembourg, The Netherlands, Poland, Portugal and Slovak Republic.
Procedure Number	UK/H/799/01-03
Timetable	Day 90 – 20th March 2006

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Omeprazole 10mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg of omeprazole.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrooesophageal reflux disease including reflux oesophagitis, maintenance treatment of reflux oesophagitis and treatment of symptoms associated with acid reflux disease.

Treatment of duodenal ulcer and benign gastric ulcers including those complicating NSAID therapy.

Treatment and maintenance treatment for relapse prevention of NSAID-related benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients who require continued NSAID treatment and have a history of gastroduodenal lesions.

Acid-related epigastric disorders (dyspepsia).

Helicobacter pylori eradication: in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.

Prophylaxis of acid aspiration.

Zollinger-Ellison syndrome.

4.2 Posology and method of administration

The capsules should be taken orally before meal (e.g. before breakfast or dinner) or on an empty stomach with a glass of water. The capsules should not be crushed or chewed.

Gastrooesophageal reflux disease including reflux oesophagitis

The usual initial dose is 20mg omeprazole once daily. Most patients heal within 4 weeks. For patients not fully healed after the initial course, healing usually occurs during additional 4-8 weeks of treatment. In patients with severe or refractory reflux oesophagitis, omeprazole can also be used at a dose of 40mg once daily. Healing usually occurs within 8 weeks.

For maintenance of healing of erosive oesophagitis the usual dose is 20mg of omeprazole once daily.

Symptomatic treatment of gastrooesophageal reflux disease: The usual dose is 10 – 20mg omeprazole once daily depending on the clinical response.

Duodenal and benign gastric ulcers
Duodenal ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 4 weeks.
Benign gastric ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 8 weeks.

In severe or recurrent cases of duodenal or benign gastric ulcer the dose may be increased to 40mg omeprazole daily.
Maintenance treatment for relapse prevention in patients with duodenal ulcer: The recommended dose is omeprazole 10 to 20mg once daily depending on the clinical response.

Treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions
The recommended dosage of omeprazole is 20mg once daily. The duration of the treatment period is 4-8 weeks.
Maintenance treatment of NSAID-related gastric ulcers, duodenal ulcers, or gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continuous NSAID treatment: The recommended dosage of omeprazole is 20mg once daily.

Acid-related dyspepsia
The recommended dose is Omeprazole 10-20mg once daily for 2-4 weeks, depending on the severity of symptoms. If a marked improvement has not occurred after 4 weeks, a further clinical examination is recommended.

Helicobacter pylori (*Hp*) eradication regimens in peptic ulcer disease
Patients with gastro-duodenal ulcers, caused by Hp infection, should be treated with omeprazole 20mg twice daily or 40mg once daily and appropriate combinations of antibiotics with adequate dosing regimens. The selection of appropriate regimen should be based on a patient's tolerability and therapeutic guidelines.

Triple therapy regimens:
- Omeprazole 20mg, amoxycillin 1g and clarithromycin 500mg. The tritherapy should be taken twice daily for one week.
- Omeprazole 20mg, clarithromycin 250mg and metronidazole 400mg (or tinidazole 500mg). The tritherapy should be taken twice daily for one week.
- Omeprazole 40mg once daily, amoxicillin 500mg three times daily and metronidazole 400mg three times daily. The tritherapy should be taken for one week.

Dual therapy regimens:
- Omeprazole 40mg daily and amoxycillin 750 to 1 g twice daily for two weeks.
- Omeprazole 40mg daily and clarithromycin 500mg three times daily for two weeks.

To ensure healing in patients with active gastric ulcers, further treatment with omeprazole monotherapy may be administered, according to the posology and treatment duration given above.

If the symptoms return and *H. pylori* eradication is unsuccessful, the therapy may be repeated or one of the alternative regimens is recommended.
For further information on the other components of the eradication therapy see individual product data sheet.

Prophylaxis of acid aspiration
For patients considered to be at risk of aspiration of the gastric contents during general anaesthesia, the recommended dose is omeprazole 40mg on the evening before surgery followed by omeprazole 40 mg 2 - 6 hours prior to surgery.

Zollinger-Ellison syndrome
Omeprazole therapy should be started at a dose of 60mg once daily. The dosage should then be adjusted individually. In more than 90% of patients a dose between 20 and 120mg daily ensures successful treatment. If doses above 80mg daily are required, they should be divided and given twice daily. Patients with Zollinger-Ellison syndrome may continue taking the drug for and indefinite period.

Elderly
Dose adjustment is not required in the elderly.

Children
The clinical experience of the use of omeprazole in children is limited. It has only been established in children over 2 years with severe ulcerating reflux oesophagitis, resistant to other treatments.

Omeprazole is recommended for healing and relieving symptoms within the dose range of 0.7 - 1.4 mg/kg daily, to a maximum of 40mg/day, for 4-12 weeks.

Weight	Daily dosage
10 – 20 kg	10mg (one capsule) – can be increased to 20mg if necessary
20 kg and above	20mg (two capsules)

Treatment should be under the supervision of a specialist (paediatrician).

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

Impaired hepatic function
As bioavailability and half-life can increase in patients with impaired hepatic function, Omeprazole should be used with caution in patients with severe liver dysfunction. The dose should be restricted to maximum 20mg daily.

Patients with swallowing difficulties
The capsules may be opened and the contents swallowed alone or added to a small amount of slightly acidic medium (orange juice or yoghurt). The granules should be swallowed immediately without chewing or crushing.

4.3 Contraindications
Known hypersensitivity to omeprazole or any of the excipients of the medicinal product.

Where a gastric ulcer is suspected, the possibility of gastric malignancy should be excluded before treatment with omeprazole is initiated as it may relieve symptoms and therefore delay diagnosis.

4.4 Special warnings and special precautions for use
Decreased gastric acidity due to omeprazole or other causes can increase gastric counts of bacteria normally present in the gastrointestinal tract and thus leads to a slightly increased risk of gastrointestinal infections such as salmonellosis or campylobacteriosis.

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

4.5 Interaction with other medicinal products and other forms of interaction
Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole treatment.

Omeprazole is metabolised in the liver through cytochrome P450 isoforms (mainly CYP 2C19, S-mephenytoin hydroxylase). By inhibiting enzymes of the CYP 2C subfamily omeprazole can delay the elimination of diazepam, phenytoin and warfarin. Although the results of clinical studies have not confirmed the interactions with warfarin and phenytoin to be clinically significant, periodic monitoring of patients is recommended since a reduction in warfarin or phenytoin dose may be necessary.

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

Concomitant treatment with omeprazole and digoxin in healthy subjects leads to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

Omeprazole can reduce the oral absorption of vitamin B_{12}. This should be taken into consideration during long-term treatment of patients with low basal values of vitamin B_{12}.

There is no evidence of interaction of omeprazole with cyclosporine, caffeine, propranolol, metoprolol, theophylline, lidocaine, quinidine, phenacetin, oestradiol, amoxycillin, diclofenac, naproxen, piroxicam, or antacids.

The absorption of omeprazole is not affected by alcohol consumption.

4.6 Pregnancy and lactation

Limited epidemiological studies showed no undesirable effects of omeprazole during pregnancy or increase in occurrence of general malformations. However, there is insufficient information on occurrence of specific malformations. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is insufficient data on infant exposure through lactation. Breastfeeding should be discontinued if the use of omeprazole is necessary.

4.7 Effects on ability to drive and use machines

No effects are foreseen.

4.8 Undesirable effects

Omeprazole is well tolerated: adverse effects can be expected to occur in 5% of patients and are usually mild, self-limiting and unrelated to dose or patient's age. They usually resolve upon discontinuation of therapy. The most common adverse effects reported are diarrhoea, dizziness, headache, constipation and skin disorders. The following have been reported from clinical trials or post marketing experience but in many cases a relationship to treatment with omeprazole has not been established.

Blood and the lymphatic system disorders
Very rare (<0.01%): Reversible leucopoenia, agranulocytosis, thrombocytopenia, and pancytopenia.

Endocrine disorders
Very rare (<0.01%): Gynaecomastia, impotence.

Metabolism disorders
Very rare (<0.01%): Hyponatraemia.

Nervous system disorders
Common (1-10%): Headache.
Uncommon (0.1-1%): Paraesthesia, somnolence, insomnia, and vertigo.
Rare (0.01-0.1%): Light-headedness and feeling faint have been associated with treatment, but all usually resolve upon discontinuation of therapy.
Very rare (<0.01%): Reversible mental confusion, agitation, hallucinations, and depressive reactions predominantly in severely ill patients.

Gastrointestinal disorders
Common (1-10%): Diarrhoea, nausea, constipation, vomiting, abdominal pain, and flatulence.
Rare (0.01-0.1%): Unpleasant taste in the mouth.
Very rare (<0.01%): Dryness of the mouth, stomatitis, and gastrointestinal candidiasis.

Hepato-biliary disorders
Uncommon (0.1-1%): Changes in liver enzyme values that are reversible upon discontinuation of the treatment.
Very rare (<0.01%): Liver failure and encelophaty in patients with pre-existing liver disease, hepatitis with or without jaundice.

Skin and subcutaneous tissue disorders
Uncommon (0.1-1%): Rash, pruritus, alopecia, erythema multiforme, bullous eruption, photosensitivity, and increased sweating.
Very rare (<0.01%): Toxic epidermal necrolysis, and Stevens-Johnson syndrome.

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

Renal disorders
Very rare (<0.01%): Interstitial nephritis and acute renal failure.

Other undesirable effects
Uncommon (0.1-1%): Peripheral oedema and blurred vision.
Very rare (<0.01%): Hypersensitivity reactions (e.g. angioedema, urticaria, bronchospasm, fever, anaphylactic shock), hyponatraemia, and malaise.

4.9 Overdose

There is no information available on the effects of overdose in humans. Single oral doses of up to 400mg have been tolerated without any severe symptoms. Elimination remained first order and no specific treatment was needed.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic class:

ATC code: A02B CO1

Pharmacotherapeutic class: selective proton pump inhibitor, substituted benzimidazole

5.1 Pharmacodynamic properties

Omeprazole belongs to a class of substituted benzimidazoles that do not exhibit anticholinergic or H_2 histamine antagonistic effects but reversibly suppress gastric acid secretion by inhibiting the enzyme H^+K^+-ATPase at the secretory surface of the gastric parietal cell. This enzyme system is considered as the acid (proton) pump and is responsible for the final step in gastric acid secretion.

Omeprazole is a weak base and is concentrated and converted to the active form omeprazole sulphenamide in the acid environment of the intracellular canaliculi within the parietal cell. Omeprazole rapidly increases pH and reduces the volume of gastric acid secretion. This effect on the final step of the gastric acid formation process is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

All pharmacodynamic effects observed are explained by the effect of omeprazole on gastric acid secretion.

After oral administration of omeprazole the onset of antisecretory effect occurs within one hour with the maximum effect occurring after 4 days of treatment. Inhibition of secretion is about 50% of maximum at 24 hours. The duration of inhibition lasts up to 72 hours and is thus longer than expected from a very short plasma half-life (less than 1 hour). The inhibitory activity increases with a repeated single dose per day, reaching a plateau after four days of treatment. After the treatment is discontinued the secretory activity returns to pre-treatment level within 3-5 days.

Omeprazole has been shown to exhibit a bactericidal effect on *Helicobacter pylori* (*Hp*) in vitro. Hp is associated with acid peptic disease including duodenal and gastric ulcers in which about 95% and 80% of patients respectively are infected with this bacterium. Most clinical data indicate that taking omeprazole 20mg twice daily in combination with two antibiotics for the period of 1 week results in >80% Hp eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower rates were observed in patients with baseline metronidazole-resistant Hp isolates. Therefore local information on the prevalence of resistance and local therapeutic guidelines should be taken into account when determining an appropriate combination regimen for Hp eradication therapy. Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief and high rates of healing of any mucosal lesions. Long-term remission of peptic ulcer disease is usually achieved thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

As a result of inhibited gastric acid secretion during long-term treatment with omeprazole an increased frequency of reversible benign gastric glandular cysts has been reported. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole is not acid-resistant and therefore it is administered orally in the form of gastro-resistant granules in hard capsules. The absorption of omeprazole begins only after the granules leave the stomach and is usually completed within 3-6 hours. Peak plasma levels are reached within 0.5 to 4.5 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 35%, and increases to about 60% after repeated once-daily administration. The plasma protein binding of omeprazole is about 95%.

Metabolism and elimination

In healthy subjects the plasma half-life of omeprazole is about 50 minutes. The inhibition of gastric acid secretion correlates with area under the plasma concentration-time curve and not to the actual plasma concentration of omeprazole at a given time.

Omeprazole is metabolised completely, mainly in the liver. The metabolites found in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

In patients with chronic renal impairment the systemic bioavailability is not significantly increased.

In patients with chronic hepatic disease the bioavailability can be greater than 90% and plasma half-life can increase up to approximately 3 hours. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children: Available data from children (1 year and older) suggest that the pharmacokinetics within the recommended doses is similar to those reported in adults. At steady state, lower plasma levels of omeprazole were seen in some children.

5.3 Preclinical safety data

There are no findings from chronic toxicity studies suggesting that any side effects unknown to date occur in humans.
Gastric enterochromaffine cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. Similar results have been observed after treatment with H_2 receptor antagonists and after partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition.
In mutagenicity studies (*in vitro* and *in vivo*) no findings of clinical relevance were observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Granules:
Low-substituted hydroxypropyl cellulose
Microcrystalline cellulose
Lactose anhydrous
Croscarmellose sodium
Povidone
Polysorbate 80
Hypromellose phthalate
Dibutyl sebacate
Talc

Capsule shell
Cap and body:
Carrageenan
Potassium chloride
Titanium dioxide
Yellow iron oxide E172
Red iron oxide E172
Hypromellose
Water
Printing ink:
Shellac
Ethyl alcohol anhydrous
Isopropyl alcohol
Propylene glycol
N-butyl alcohol
Ammonium hydroxide
Potassium hydroxide
Purified water
Black iron oxide E172

6.2. Incompatibilities
None applicable.

6.3. Shelf life
2 years

6.4. Special precautions for storage
Do not store above 30°C.
Store in the original package.
Keep the bottle tightly closed.

6.5. Nature and contents of container
Alu/Alu blister packs of 7, 14, 15, 28, 30, 56, 56x1 and 98 capsules.

Plastic bottles (white, high density polyethylene), PP cap, desiccant (polyethylene capsules with molecular sieves, printed) in boxes of 30 capsules.

Glass bottles (amber moulded glass, hydrolytic class III), screw cap (high density polyethylene, with inserted desiccant agent silica gel 20%, molecular sieves 80%) in boxes of 15 capsules.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)
No special requirements

7. MARKETING AUTHORISATION HOLDER
Sandoz Ltd
37 Woolmer Way, Bordon,
Hampshire
GU35 9QE
United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 04416/0651

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
3rd March 2005

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Omeprazole 20mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg of omeprazole.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrooesophageal reflux disease including reflux oesophagitis, maintenance treatment of reflux oesophagitis and treatment of symptoms associated with acid reflux disease.

Treatment of duodenal ulcer and benign gastric ulcers including those complicating NSAID therapy.

Treatment and maintenance treatment for relapse prevention of NSAID-related benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients who require continued NSAID treatment and have a history of gastroduodenal lesions.

Acid-related epigastric disorders (dyspepsia).
Helicobacter pylori eradication: in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.

Prophylaxis of acid aspiration.

Zollinger-Ellison syndrome.

4.2 Posology and method of administration

The capsules should be taken orally before meal (e.g. before breakfast or dinner) or on an empty stomach with a glass of water. The capsules should not be crushed or chewed.

Gastrooesophageal reflux disease including reflux oesophagitis

The usual initial dose is 20mg omeprazole once daily. Most patients heal within 4 weeks. For patients not fully healed after the initial course, healing usually occurs during additional 4-8 weeks of treatment. In patients with severe or refractory reflux oesophagitis, omeprazole can also be used at a dose of 40mg once daily. Healing usually occurs within 8 weeks.

For maintenance of healing of erosive oesophagitis the usual dose is 20mg of omeprazole once daily.

Symptomatic treatment of gastrooesophageal reflux disease: The usual dose is 10 – 20mg omeprazole once daily depending on the clinical response.
Duodenal and benign gastric ulcers
Duodenal ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 4 weeks.

Benign gastric ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 8 weeks.

In severe or recurrent cases of duodenal or benign gastric ulcer the dose may be increased to 40mg omeprazole daily.

Maintenance treatment for relapse prevention in patients with duodenal ulcer: The recommended dose is omeprazole 10 to 20mg once daily depending on the clinical response.

Treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions

The recommended dosage of omeprazole is 20mg once daily. The duration of the treatment period is 4-8 weeks.

Maintenance treatment of NSAID-related gastric ulcers, duodenal ulcers, or gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continuous NSAID treatment: The recommended dosage of omeprazole is 20mg once daily.

Acid-related dyspepsia
The recommended dose is Omeprazole 10-20mg once daily for 2-4 weeks, depending on the severity of symptoms. If a marked improvement has not occurred after 4 weeks, a further clinical examination is recommended.

Helicobacter pylori (*Hp*) eradication regimens in peptic ulcer disease
Patients with gastro-duodenal ulcers, caused by Hp infection, should be treated with omeprazole 20mg twice daily or 40mg once daily and appropriate combinations of antibiotics with adequate dosing regimens. The selection of appropriate regimen should be based on a patient's tolerability and therapeutic guidelines.

Triple therapy regimens:
- Omeprazole 20mg, amoxycillin 1g and clarithromycin 500mg. The tritherapy should be taken twice daily for one week.
- Omeprazole 20mg, clarithromycin 250mg and metronidazole 400mg (or tinidazole 500mg). The tritherapy should be taken twice daily for one week.
- Omeprazole 40mg once daily, amoxicillin 500mg three times daily and metronidazole 400mg three times daily. The tritherapy should be taken for one week.

Dual therapy regimens:
- Omeprazole 40mg daily and amoxycillin 750 to 1 g twice daily for two weeks.
- Omeprazole 40mg daily and clarithromycin 500mg three times daily for two weeks.

To ensure healing in patients with active gastric ulcers, further treatment with omeprazole monotherapy may be administered, according to the posology and treatment duration given above.

If the symptoms return and *H. pylori* eradication is unsuccessful, the therapy may be repeated or one of the alternative regimens is recommended.

For further information on the other components of the eradication therapy see individual product data sheet.

Prophylaxis of acid aspiration
For patients considered to be at risk of aspiration of the gastric contents during general anaesthesia, the recommended dose is omeprazole 40mg on the evening before surgery followed by omeprazole 40 mg 2 - 6 hours prior to surgery.

Zollinger-Ellison syndrome
Omeprazole therapy should be started at a dose of 60mg once daily. The dosage should then be adjusted individually. In more than 90% of patients a dose between 20 and 120mg daily ensures successful treatment. If doses above 80mg daily are required, they should be divided and given twice daily. Patients with Zollinger-Ellison syndrome may continue taking the drug for and indefinite period.

Elderly
Dose adjustment is not required in the elderly.

Children
The clinical experience of the use of omeprazole in children is limited. It has only been established in children over 2 years with severe ulcerating reflux oesophagitis, resistant to other treatments.

Omeprazole is recommended for healing and relieving symptoms within the dose range of 0.7 - 1.4 mg/kg daily, to a maximum of 40mg/day, for 4-12 weeks.

Weight	Daily dosage
10 – 20 kg	10mg (one capsule) – can be increased to 20mg if necessary
20 kg and above	20mg (two capsules)

Treatment should be under the supervision of a specialist (paediatrician).

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

Impaired hepatic function
As bioavailability and half-life can increase in patients with impaired hepatic function, Omeprazole should be used with caution in patients with severe liver dysfunction. The dose should be restricted to maximum 20mg daily.

Patients with swallowing difficulties
The capsules may be opened and the contents swallowed alone or added to a small amount of slightly acidic medium (orange juice or yoghurt). The granules should be swallowed immediately without chewing or crushing.

4.3 Contraindications
Known hypersensitivity to omeprazole or any of the excipients of the medicinal product.

Where a gastric ulcer is suspected, the possibility of gastric malignancy should be excluded before treatment with omeprazole is initiated as it may relieve symptoms and therefore delay diagnosis.

4.4 Special warnings and special precautions for use
Decreased gastric acidity due to omeprazole or other causes can increase gastric counts of bacteria normally present in the gastrointestinal tract and thus leads to a slightly increased risk of gastrointestinal infections such as salmonellosis or campylobacteriosis.

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

4.5 Interaction with other medicinal products and other forms of interaction
Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole treatment.

Omeprazole is metabolised in the liver through cytochrome P450 isoforms (mainly CYP 2C19, S-mephenytoin hydroxylase). By inhibiting enzymes of the CYP 2C subfamily omeprazole can delay the elimination of diazepam, phenytoin and warfarin. Although the results of clinical studies have not confirmed the interactions with warfarin and phenytoin to be clinically significant, periodic monitoring of patients is recommended since a reduction in warfarin or phenytoin dose may be necessary.

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

Concomitant treatment with omeprazole and digoxin in healthy subjects leads to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

Omeprazole can reduce the oral absorption of vitamin B_{12}. This should be taken into consideration during long-term treatment of patients with low basal values of vitamin B_{12}.

There is no evidence of interaction of omeprazole with cyclosporine, caffeine, propranolol, metoprolol, theophylline, lidocaine, quinidine, phenacetin, oestradiol, amoxycillin, diclofenac, naproxen, piroxicam, or antacids.

The absorption of omeprazole is not affected by alcohol consumption.

4.6 Pregnancy and lactation
Limited epidemiological studies showed no undesirable effects of omeprazole during pregnancy or increase in occurrence of general malformations. However, there is insufficient information on occurrence of specific malformations. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is insufficient data on infant exposure through lactation. Breastfeeding should be discontinued if the use of omeprazole is necessary.

4.7 Effects on ability to drive and use machines

No effects are foreseen.

4.8 Undesirable effects

Omeprazole is well tolerated: adverse effects can be expected to occur in 5% of patients and are usually mild, self-limiting and unrelated to dose or patient's age. They usually resolve upon discontinuation of therapy. The most common adverse effects reported are diarrhoea, dizziness, headache, constipation and skin disorders. The following have been reported from clinical trials or post marketing experience but in many cases a relationship to treatment with omeprazole has not been established.

Blood and the lymphatic system disorders
Very rare (<0.01%): Reversible leucopoenia, agranulocytosis, thrombocytopenia, and pancytopenia.

Endocrine disorders
Very rare (<0.01%): Gynaecomastia, impotence.

Metabolism disorders
Very rare (<0.01%): Hyponatraemia.

Nervous system disorders
Common (1-10%): Headache.
Uncommon (0.1-1%): Paraesthesia, somnolence, insomnia, and vertigo.
Rare (0.01-0.1%): Light-headedness and feeling faint have been associated with treatment, but all usually resolve upon discontinuation of therapy.
Very rare (<0.01%): Reversible mental confusion, agitation, hallucinations, and depressive reactions predominantly in severely ill patients.

Gastrointestinal disorders
Common (1-10%): Diarrhoea, nausea, constipation, vomiting, abdominal pain, and flatulence.
Rare (0.01-0.1%): Unpleasant taste in the mouth.
Very rare (<0.01%): Dryness of the mouth, stomatitis, and gastrointestinal candidiasis.

Hepato-biliary disorders
Uncommon (0.1-1%): Changes in liver enzyme values that are reversible upon discontinuation of the treatment.
Very rare (<0.01%): Liver failure and encelophaty in patients with pre-existing liver disease, hepatitis with or without jaundice.

Skin and subcutaneous tissue disorders
Uncommon (0.1-1%): Rash, pruritus, alopecia, erythema multiforme, bullous eruption, photosensitivity, and increased sweating.
Very rare (<0.01%): Toxic epidermal necrolysis, and Stevens-Johnson syndrome.

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

Renal disorders
Very rare (<0.01%): Interstitial nephritis and acute renal failure.

Other undesirable effects
Uncommon (0.1-1%): Peripheral oedema and blurred vision.
Very rare (<0.01%): Hypersensitivity reactions (e.g. angioedema, urticaria, bronchospasm, fever, anaphylactic shock), hyponatraemia, and malaise.

4.9 Overdose

There is no information available on the effects of overdose in humans. Single oral doses of up to 400mg have been tolerated without any severe symptoms. Elimination remained first order and no specific treatment was needed.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic class:
ATC code: A02B CO1

Pharmacotherapeutic class: selective proton pump inhibitor, substituted benzimidazole

5.1 Pharmacodynamic properties

Omeprazole belongs to a class of substituted benzimidazoles that do not exhibit anticholinergic or H_2 histamine antagonistic effects but reversibly suppress gastric acid secretion by inhibiting the enzyme H^+K^+-ATPase at the secretory surface of the gastric parietal cell. This enzyme system is considered as the acid (proton) pump and is responsible for the final step in gastric acid secretion.

Omeprazole is a weak base and is concentrated and converted to the active form omeprazole sulphenamide in the acid environment of the intracellular canaliculi within the parietal cell. Omeprazole rapidly increases pH and reduces the volume of gastric acid secretion. This effect on the final step of the gastric acid formation process is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

All pharmacodynamic effects observed are explained by the effect of omeprazole on gastric acid secretion.

After oral administration of omeprazole the onset of antisecretory effect occurs within one hour with the maximum effect occurring after 4 days of treatment. Inhibition of secretion is about 50% of maximum at 24 hours. The duration of inhibition lasts up to 72 hours and is thus longer than expected from a very short plasma half-life (less than 1 hour). The inhibitory activity increases with a repeated single dose per day, reaching a plateau after four days of treatment. After the treatment is discontinued the secretory activity returns to pre-treatment level within 3-5 days.

Omeprazole has been shown to exhibit a bactericidal effect on *Helicobacter pylori* (*Hp*) in vitro. Hp is associated with acid peptic disease including duodenal and gastric ulcers in which about 95% and 80% of patients respectively are infected with this bacterium. Most clinical data indicate that taking omeprazole 20mg twice daily in combination with two antibiotics for the period of 1 week results in >80% Hp eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower rates were observed in patients with baseline metronidazole-resistant Hp isolates. Therefore local information on the prevalence of resistance and local therapeutic guidelines should be taken into account when determining an appropriate combination regimen for Hp eradication therapy. Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief and high rates of healing of any mucosal lesions. Long-term remission of peptic ulcer disease is usually achieved thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

As a result of inhibited gastric acid secretion during long-term treatment with omeprazole an increased frequency of reversible benign gastric glandular cysts has been reported. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole is not acid-resistant and therefore it is administered orally in the form of gastro-resistant granules in hard capsules. The absorption of omeprazole begins only after the granules leave the stomach and is usually completed within 3-6 hours. Peak plasma levels are reached within 0.5 to 4.5 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 35%, and increases to about 60% after repeated once-daily administration. The plasma protein binding of omeprazole is about 95%.

Metabolism and elimination

In healthy subjects the plasma half-life of omeprazole is about 50 minutes. The inhibition of gastric acid secretion correlates with area under the plasma concentration-time curve and not to the actual plasma concentration of omeprazole at a given time.

Omeprazole is metabolised completely, mainly in the liver. The metabolites found in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

In patients with chronic renal impairment the systemic bioavailability is not significantly increased.

In patients with chronic hepatic disease the bioavailability can be greater than 90% and plasma half-life can increase up to approximately 3 hours. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children: Available data from children (1 year and older) suggest that the pharmacokinetics within the recommended doses is similar to those reported in adults. At steady state, lower plasma levels of omeprazole were seen in some children.

5.3 Preclinical safety data

There are no findings from chronic toxicity studies suggesting that any side effects unknown to date occur in humans.

Gastric enterochromaffine cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. Similar results have been observed after treatment with H_2 receptor antagonists and after partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition.

In mutagenicity studies (*in vitro* and *in vivo*) no findings of clinical relevance were observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Granules:
Low-substituted hydroxypropyl cellulose
Microcrystalline cellulose
Lactose anhydrous
Croscarmellose sodium
Povidone
Polysorbate 80
Hypromellose phthalate
Dibutyl sebacate
Talc

Capsule shell
Cap and body:
Carrageenan
Potassium chloride
Titanium dioxide
Hypromellose
Water

Printing ink:
Shellac
Ethyl alcohol anhydrous
Isopropyl alcohol
Propylene glycol
N-butyl alcohol
Ammonium hydroxide
Potassium hydroxide
Purified water
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.
Keep the bottle tightly closed.

6.5. Nature and contents of container

Alu/Alu blister packs of 7, 14, 15, 28, 30, 56, 56x1 and 98 capsules.

Plastic bottles (white, high density polyethylene), PP cap, desiccant (polyethylene capsules with molecular sieves, printed) in boxes of 30 and 100 capsules.

Glass bottles (amber moulded glass, hydrolytic class III), screw cap (high density polyethylene, with inserted desiccant agent silica gel 20%, molecular sieves 80%) in boxes of 15 capsules.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

No special requirements

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd
37 Woolmer Way,
Bordon, Hampshire
GU35 9QE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04416/0652

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3rd March 2005

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Omeprazole 40 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg of omeprazole.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Capsules
White cap, light brown body, each imprinted with “OME 40” containing dull yellowish brown pellets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrooesophageal reflux disease including reflux oesophagitis.

Treatment of duodenal ulcer and benign gastric ulcers including those complicating NSAID therapy.

Helicobacter pylori eradication: in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.

Prophylaxis of acid aspiration.

Zollinger-Ellison syndrome.

4.2 Posology and method of administration

The capsules should be taken orally before meal (e.g. before breakfast or dinner) or on an empty stomach with a glass of water. The capsules should not be crushed or chewed.

Gastrooesophageal reflux disease including reflux oesophagitis

The usual initial dose is 20mg omeprazole once daily. Most patients heal within 4 weeks. For patients not fully healed after the initial course, healing usually occurs during additional 4-8 weeks of treatment. In patients with severe or refractory reflux oesophagitis, omeprazole can also be used at a dose of 40mg once daily. Healing usually occurs within 8 weeks.

For maintenance of healing of erosive oesophagitis the usual dose is 20mg of omeprazole once daily.

Symptomatic treatment of gastrooesophageal reflux disease: The usual dose is 10 – 20mg omeprazole once daily depending on the clinical response.

Duodenal and benign gastric ulcers
Duodenal ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 4 weeks.
Benign gastric ulcer: The usual dose is 20mg omeprazole once daily. Most patients heal within 8 weeks.
In severe or recurrent cases of duodenal or benign gastric ulcer the dose may be increased to 40mg omeprazole daily.
Maintenance treatment for relapse prevention in patients with duodenal ulcer: The recommended dose is omeprazole 10 to 20mg once daily depending on the clinical response.

Helicobacter pylori (*Hp*) eradication regimens in peptic ulcer disease
Patients with gastro-duodenal ulcers, caused by Hp infection, should be treated with omeprazole 20mg twice daily or 40mg once daily and appropriate combinations of antibiotics with adequate dosing regimens. The selection of appropriate regimen should be based on a patient’s tolerability and therapeutic guidelines.

Triple therapy regimens:
- Omeprazole 20mg, amoxycillin 1g and clarithromycin 500mg. The tritherapy should be taken twice daily for one week.
- Omeprazole 20mg, clarithromycin 250mg and metronidazole 400mg (or tinidazole 500mg). The tritherapy should be taken twice daily for one week.
- Omeprazole 40mg once daily, amoxicillin 500mg three times daily and metronidazole 400mg three times daily. The tritherapy should be taken for one week.

Dual therapy regimens:
- Omeprazole 40mg daily and amoxycillin 750 to 1 g twice daily for two weeks.
- Omeprazole 40mg daily and clarithromycin 500mg three times daily for two weeks.

To ensure healing in patients with active gastric ulcers, further treatment with omeprazole monotherapy may be administered, according to the posology and treatment duration given above.

If the symptoms return and *H. pylori* eradication is unsuccessful, the therapy may be repeated or one of the alternative regimens is recommended.
For further information on the other components of the eradication therapy see individual product data sheet.

Prophylaxis of acid aspiration
For patients considered to be at risk of aspiration of the gastric contents during general anaesthesia, the recommended dose is omeprazole 40mg on the evening before surgery followed by omeprazole 40 mg 2 - 6 hours prior to surgery.

Zollinger-Ellison syndrome
Omeprazole therapy should be started at a dose of 60mg once daily. The dosage should then be adjusted individually. In more than 90% of patients a dose between 20 and 120mg daily ensures successful treatment. If doses above 80mg daily are required, they should be divided and given twice daily. Patients with Zollinger-Ellison syndrome may continue taking the drug for and indefinite period.

Elderly
Dose adjustment is not required in the elderly.

Children
The clinical experience of the use of omeprazole in children is limited. It has only been established in children over 2 years with severe ulcerating reflux oesophagitis, resistant to other treatments.

Omeprazole is recommended for healing and relieving symptoms within the dose range of 0.7 - 1.4 mg/kg daily, to a maximum of 40mg/day, for 4-12 weeks.

Weight	Daily dosage
10 – 20 kg	10mg (one capsule) – can be increased to 20mg if necessary
20 kg and above	20mg (two capsules)

Treatment should be under the supervision of a specialist (paediatrician).

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

Impaired hepatic function
As bioavailability and half-life can increase in patients with impaired hepatic function, Omeprazole should be used with caution in patients with severe liver dysfunction. The dose should be restricted to maximum 20mg daily.

Patients with swallowing difficulties
The capsules may be opened and the contents swallowed alone or added to a small amount of slightly acidic medium (orange juice or yoghurt). The granules should be swallowed immediately without chewing or crushing.

4.3 Contraindications
Known hypersensitivity to omeprazole or any of the excipients of the medicinal product.

Where a gastric ulcer is suspected, the possibility of gastric malignancy should be excluded before treatment with omeprazole is initiated as it may relieve symptoms and therefore delay diagnosis.

4.4 Special warnings and special precautions for use
Decreased gastric acidity due to omeprazole or other causes can increase gastric counts of bacteria normally present in the gastrointestinal tract and thus leads to a slightly increased risk of gastrointestinal infections such as salmonellosis or campylobacteriosis.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole treatment.

Omeprazole is metabolised in the liver through cytochrome P450 isoforms (mainly CYP 2C19, S-mephenytoin hydroxylase). By inhibiting enzymes of the CYP 2C subfamily omeprazole can delay the elimination of diazepam, phenytoin and warfarin. Although the results of clinical studies have not confirmed the interactions with warfarin and phenytoin to be clinically significant, periodic monitoring of patients is recommended since a reduction in warfarin or phenytoin dose may be necessary.

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

Concomitant treatment with omeprazole and digoxin in healthy subjects leads to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

Omeprazole can reduce the oral absorption of vitamin B_{12}. This should be taken into consideration during long-term treatment of patients with low basal values of vitamin B_{12}.

There is no evidence of interaction of omeprazole with cyclosporine, caffeine, propranolol, metoprolol, theophylline, lidocaine, quinidine, phenacetin, oestradiol, amoxycillin, diclofenac, naproxen, piroxicam, or antacids.

The absorption of omeprazole is not affected by alcohol consumption.

4.6 Pregnancy and lactation

Limited epidemiological studies showed no undesirable effects of omeprazole during pregnancy or increase in occurrence of general malformations. However, there is insufficient information on occurrence of specific malformations. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is insufficient data on infant exposure through lactation. Breastfeeding should be discontinued if the use of omeprazole is necessary.

4.7 Effects on ability to drive and use machines

No effects are foreseen.

4.8 Undesirable effects

Omeprazole is well tolerated: adverse effects can be expected to occur in 5% of patients and are usually mild, self-limiting and unrelated to dose or patient's age. They usually resolve upon discontinuation of therapy. The most common adverse effects reported are diarrhoea, dizziness, headache, constipation and skin disorders. The following have been reported from clinical trials or post marketing experience but in many cases a relationship to treatment with omeprazole has not been established.

Blood and the lymphatic system disorders
Very rare (<0.01%): Reversible leucopoenia, agranulocytosis, thrombocytopenia, and pancytopenia.

Endocrine disorders
Very rare (<0.01%): Gynaecomastia, impotence.

Metabolism disorders
Very rare (<0.01%): Hyponatraemia.

Nervous system disorders
Common (1-10%): Headache.
Uncommon (0.1-1%): Paraesthesia, somnolence, insomnia, and vertigo.

Rare (0.01-0.1%): Light-headedness and feeling faint have been associated with treatment, but all usually resolve upon discontinuation of therapy.
Very rare (<0.01%): Reversible mental confusion, agitation, hallucinations, and depressive reactions predominantly in severely ill patients.

Gastrointestinal disorders
Common (1-10%): Diarrhoea, nausea, constipation, vomiting, abdominal pain, and flatulence.
Rare (0.01-0.1%): Unpleasant taste in the mouth.
Very rare (<0.01%): Dryness of the mouth, stomatitis, and gastrointestinal candidiasis.

Hepato-biliary disorders
Uncommon (0.1-1%): Changes in liver enzyme values that are reversible upon discontinuation of the treatment.
Very rare (<0.01%): Liver failure and encelophaty in patients with pre-existing liver disease, hepatitis with or without jaundice.

Skin and subcutaneous tissue disorders
Uncommon (0.1-1%): Rash, pruritus, alopecia, erythema multiforme, bullous eruption, photosensitivity, and increased sweating.
Very rare (<0.01%): Toxic epidermal necrolysis, and Stevens-Johnson syndrome.

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

Renal disorders
Very rare (<0.01%): Interstitial nephritis and acute renal failure.

Other undesirable effects
Uncommon (0.1-1%): Peripheral oedema and blurred vision.
Very rare (<0.01%): Hypersensitivity reactions (e.g. angioedema, urticaria, bronchospasm, fever, anaphylactic shock), hyponatraemia, and malaise.

4.9 Overdose

There is no information available on the effects of overdose in humans. Single oral doses of up to 400mg have been tolerated without any severe symptoms. Elimination remained first order and no specific treatment was needed.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic class:
ATC code: A02B CO1
Pharmacotherapeutic class: selective proton pump inhibitor, substituted benzimidazole

5.1 Pharmacodynamic properties

Omeprazole belongs to a class of substituted benzimidazoles that do not exhibit anticholinergic or H_2 histamine antagonistic effects but reversibly suppress gastric acid secretion by inhibiting the enzyme H^+K^+-ATPase at the secretory surface of the gastric parietal cell. This enzyme system is considered as the acid (proton) pump and is responsible for the final step in gastric acid secretion.

Omeprazole is a weak base and is concentrated and converted to the active form omeprazole sulphenamide in the acid environment of the intracellular canaliculi within the parietal cell. Omeprazole rapidly increases pH and reduces the volume of gastric acid secretion. This effect on the final step of the gastric acid formation process is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

All pharmacodynamic effects observed are explained by the effect of omeprazole on gastric acid secretion.

After oral administration of omeprazole the onset of antisecretory effect occurs within one hour with the maximum effect occurring after 4 days of treatment. Inhibition of secretion is about 50% of maximum at 24 hours. The duration of inhibition lasts up to 72 hours and is thus longer than expected from a very short plasma half-life (less than 1 hour). The inhibitory activity increases with a repeated single dose per day, reaching a plateau after four days of treatment. After the treatment is discontinued the secretory activity returns to pre-treatment level within 3-5 days.

Omeprazole has been shown to exhibit a bactericidal effect on *Helicobacter pylori* (*Hp*) in vitro. Hp is associated with acid peptic disease including duodenal and gastric ulcers in which about 95% and 80% of patients respectively are infected with this bacterium. Most clinical data indicate that taking omeprazole 20mg twice daily in combination with two antibiotics for the period of 1 week results in >80% Hp eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower rates were observed in patients with baseline metronidazole-resistant Hp isolates. Therefore local information on the prevalence of resistance and local therapeutic guidelines should be taken into account when determining an appropriate combination regimen for Hp eradication therapy. Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief and high rates of healing of any mucosal lesions. Long-term remission of peptic ulcer disease is usually achieved thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

As a result of inhibited gastric acid secretion during long-term treatment with omeprazole an increased frequency of reversible benign gastric glandular cysts has been reported. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole is not acid-resistant and therefore it is administered orally in the form of gastro-resistant granules in hard capsules. The absorption of omeprazole begins only after the granules leave the stomach and is usually completed within 3-6 hours. Peak plasma levels are reached within 0.5 to 4.5 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 35%, and increases to about 60% after repeated once-daily administration. The plasma protein binding of omeprazole is about 95%.

Metabolism and elimination

In healthy subjects the plasma half-life of omeprazole is about 50 minutes. The inhibition of gastric acid secretion correlates with area under the plasma concentration-time curve and not to the actual plasma concentration of omeprazole at a given time.

Omeprazole is metabolised completely, mainly in the liver. The metabolites found in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

In patients with chronic renal impairment the systemic bioavailability is not significantly increased.

In patients with chronic hepatic disease the bioavailability can be greater than 90% and plasma half-life can increase up to approximately 3 hours. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children: Available data from children (1 year and older) suggest that the pharmacokinetics within the recommended doses is similar to those reported in adults. At steady state, lower plasma levels of omeprazole were seen in some children.

5.3 Preclinical safety data

There are no findings from chronic toxicity studies suggesting that any side effects unknown to date occur in humans.

Gastric enterochromaffine cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. Similar results have been observed after treatment with H_2 receptor antagonists and after partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition.

In mutagenicity studies (*in vitro* and *in vivo*) no findings of clinical relevance were observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pellets:

Low-substituted hydroxypropyl cellulose

Microcrystalline cellulose

Lactose anhydrous
Croscarmellose sodium
Povidone
Polysorbate 80
Hypromellose phthalate
Dibutyl sebacate
Talc

Capsule shell
Cap:
Carrageenan
Potassium chloride
Titanium dioxide
Hypromellose
Water
Body:
Carrageenan
Potassium chloride
Titanium dioxide
Hypromellose
Red iron oxide E172
Yellow iron oxide E172
Water

Printing ink:
Shellac
Ethyl alcohol anhydrous
Isopropyl alcohol
Propylene glycol
N-butyl alcohol
Ammonium hydroxide
Potassium hydroxide
Purified water
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.
Keep the bottle tightly closed.

6.5. Nature and contents of container
Alu/Alu blister packs of 7, 14, 15, 28, 30, 56, and 98 capsules.

Plastic bottles (white, high density polyethylene), PP cap, desiccant (polyethylene capsules with molecular sieves, printed) in boxes of 30 capsules.

Glass bottles (amber moulded glass, hydrolytic class III), screw cap (high density polyethylene, with inserted desiccant agent silica gel 20%, molecular sieves 80%) in boxes of 15 capsules.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)
No special requirements

7. MARKETING AUTHORISATION HOLDER
Sandoz Ltd
37 Woolmer Way,

Bordon,
Hampshire
GU35 9QE

8. MARKETING AUTHORISATION NUMBER

PL 04416/0653

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4th March 2005

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet

SANDOZ

PATIENT INFORMATION LEAFLET

SZ90708LT01D

Omeprazole 10mg, 20mg and 40mg Capsules

Please read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The name of your medicine is **Omeprazole 10mg, 20mg and 40mg Capsules.**
The active substance is omeprazole.
The other ingredients in these gastro-resistant granules are low-substituted hydroxypropyl cellulose, microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, povidone, polysorbate 80, hypromellose phthalate, dibutyl sebacate and talc.
The capsule shell ingredients are carrageenan, potassium chloride, titanium dioxide, hypromellose and iron oxides E172 (red and yellow in 10mg and 40mg capsules, respectively).
Black printing ink: shellac, propylene glycol, ammonium hydroxide, potassium hydroxide and black iron oxide E172.

The Marketing Authorisation Holder is: Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE.
The Manufacturer is: Lek Pharmaceuticals d.d., Verovskova 57, Ljubljana, Slovenia.

1. WHAT OMEPRAZOLE CAPSULES ARE AND WHAT THEY ARE USED FOR

Each capsule contains 10mg, 20mg or 40mg of omeprazole as gastro-resistant granules.
The 10mg capsules are light brown cap, light brown body, each imprinted with "OME 10" and contain dull yellowish brown granules.
The 20mg capsules are white cap, white body, each imprinted with "OME 20" and contain dull yellowish brown granules.
The 40mg capsules are white cap, light brown body, each imprinted with "OME 40" and contain dull yellowish brown granules.

Package sizes
Blister packs of 7, 14, 15, 28, 30, 56, 56x1 or 98 capsules.
Plastic bottles of 30 or 100 capsules.
Glass bottles of 15 capsules.

What is Omeprazole used for?
Omeprazole belongs to a group of medicinal products called proton pump inhibitors. They reduce the amount of acid that your stomach makes. This allows the ulcers to heal and eases the pain.
Omeprazole Capsules are used for treating people diagnosed as having:
- Acid that has escaped from the stomach into the gullet causing heartburn, pain, and inflammation. This condition is called gastro-oesophageal reflux disease (GORD) or reflux oesophagitis.
- Acid indigestion (dyspepsia) that causes stomach pain or discomfort.
- Ulcers in the stomach (gastric ulcer) or upper part of the intestine (duodenal ulcer), which may or may have not been caused by taking a non-steroidal anti-inflammatory drug (NSAID). If you have a history of ulcer problems and need to continue taking a NSAID, Omeprazole Capsules may be used to heal your ulcer or prevent one developing.
- Ulcers that are infected by bacteria called Helicobacter pylori.
- Prevention of damage to the lungs caused by breathing in stomach fluid (acid aspiration). For instance, it may be used before an operation.
- Excess acid in the stomach produced by a growth in the pancreas (Zollinger-Ellisson syndrome).

2. BEFORE YOU TAKE OMEPRAZOLE CAPSULES

Do not take Omeprazole Capsules if:
- You are hypersensitive (allergic) to omeprazole or any of the other ingredients in Omeprazole Capsules.

Special precautions for use
Tell your doctor before you start to take this medicine:
- If you have any liver diseases - your doctor may wish to reduce the dose of Omeprazole Capsules to 20mg daily.
- If you have any other medical conditions including blood problems (e.g. anaemia, vitamin B_{12} deficiency).

Pregnancy and breast-feeding
The safety of omeprazole use during pregnancy and breast-feeding has not been entirely confirmed. Pregnant women and nursing mothers should not take Omeprazole Capsules without consulting their doctor.

Driving and using machines
Omeprazole Capsules do not affect the ability to drive and use machinery.

Important information about the ingredients of Omeprazole Capsules
Omeprazole Capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Taking other medicines
Tell your doctor about any medicine you are taking, or have recently taken - even those not prescribed.
It's especially important to tell your doctor if you are taking any of the following medicines: diazepam (for your nerves), phenytoin (for epilepsy), warfarin (for thinning the blood), digoxin (for your heart), ketoconazole or itraconazole (for treating fungal infections), vitamin B_{12} supplements.
These medicines may be affected by Omeprazole Capsules or may affect how well it works. Your doctor may wish to reduce the dose of Omeprazole Capsules or other medicines.
If you take Omeprazole Capsules for a long time it may lower your vitamin B_{12} level. Your doctor may carry out an annual check on your vitamin B_{12} level.

3. HOW TO TAKE OMEPRAZOLE CAPSULES

Omeprazole Capsules can be taken by adults including the elderly. They can also be taken by children over 2 years having severe heartburn, when other treatments have not worked.

Take this medicine before eating or on an empty stomach. Swallow the capsules whole, with a drink of water. Do not crush or chew the capsules. If you have trouble swallowing them, open the capsules and mix the granules with fruit juice or yoghurt and drink immediately.

If you are taking Omeprazole Capsules once daily, try to take them at about the same time each day. If you are taking Omeprazole Capsules twice daily, the first dose should be in the morning and the second dose in the evening.

Your doctor will tell you how many capsules to take and how long your treatment with Omeprazole Capsules will last. The strength of the capsules and the length of time you have to take them for will depend on the condition you are suffering from.

Treatment of heartburn (reflux oesophagitis and gastro-oesophageal reflux disease): For adults the usual dose is Omeprazole Capsules 20mg once daily for 4 weeks. Your doctor may tell you to continue taking the capsules for another 4 or 8 weeks or increase the dose to 40mg of Omeprazole Capsules daily. To prevent the heartburn returning, your doctor may tell you to continue taking Omeprazole Capsules 20mg.

Treatment of children with severe form of reflux oesophagitis: The dose for children over 2 years with severe heartburn will depend on their weight; the treatment should last 4-12 weeks.

Weight	Daily Dosage
10 - 20kg	10mg (one capsule) - can be increased to 20mg if necessary
20kg and above	20mg (two capsules)

Relief of acid indigestion (dyspepsia): The usual dose is Omeprazole Capsules 10mg or 20mg once daily for 2-4 weeks. If your symptoms do not resolve or they return, consult your doctor.

Treatment of stomach ulcers (gastric ulcer) and ulcers in the upper part of the intestine (duodenal ulcer): The usual dose is Omeprazole Capsules 20mg once daily for 4-8 weeks. Omeprazole Capsules 40mg may be used if your ulcer is severe. To prevent your upper intestinal ulcer returning Omeprazole Capsules 10mg or 20mg may be used.

Treatment and prevention of stomach and duodenal ulcers and associated symptoms caused by NSAIDs: If you have previously had an ulcer and need to continue taking a NSAID, the only recommended dose is Omeprazole Capsules 20mg once daily. Your doctor will tell you how long to take your capsules for.

Treatment of ulcers caused by infection with bacteria Helicobacter pylori: The usual dose is Omeprazole Capsules 40mg once daily or 20mg twice daily. Your doctor will tell you to take one or a combination of two antibiotics (amoxicillin, clarithromycin, metronidazole or tinidazole) at the same time. The treatment usually lasts 1 or 2 weeks. Follow the instructions for taking your medicine carefully. If you are unsure about anything, ask your doctor.

Before a hospital operation when you are to be given a general anaesthetic: The usual dose is Omeprazole Capsules 40mg the evening before surgery, and then another Omeprazole Capsules 40mg two to six hours before surgery.

Treatment for excess acid in the stomach caused by the growth in the pancreas (Zollinger-Ellisson syndrome): The usual starting dose is Omeprazole Capsules 60mg once daily. If the dose is more than 80mg daily, half the dose should be taken in the morning and half in the evening.

If you take more Omeprazole Capsules than you should: If you have taken one extra dose this is unlikely to cause problems. If you, or someone else, has taken more than one extra dose or a large overdose of Omeprazole Capsules, contact your doctor or local hospital accident and emergency department immediately.

If you forget to take Omeprazole Capsules: If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, do not take the missed dose, just take the next dose on time.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Omeprazole Capsules can have side effects. They are usually mild and go away when you stop taking this medicine.

Most commonly you might get diarrhoea, dizziness, headache, constipation, skin rash or itchy skin. Less commonly you can feel sick, get wind, stomach ache, feeling faint or pins and needles. You can be at slightly increased risk for gut infection.

Other very rare side effects you might have are: sensitivity to light, severe allergic skin reactions with skin blistering, swollen lips, swelling or soreness of the mouth and throat, dry mouth, mood changes, low blood sodium, hair loss, changes in sleep patterns, sore joints and muscles, blurred vision, swollen limbs, increased sweating, larger breasts (males), impotence, blood or taste disorders, a high temperature, difficulty in breathing, kidney or liver problems. If you are very ill, you might feel confused, nervous, depressed, or get hallucinations. It is not known if these side effects are caused directly by Omeprazole Capsules.

You should contact your doctor immediately or go to the casualty department at your nearest hospital if you develop any allergic reaction, unexplained sore throat, fever, any urinary problems, or jaundice (yellowish colouration of the eyes or nail-beds and greenish-yellow colour of urine).

If you suffer from any of these side effects, or if you get any other unusual or unexpected symptoms not mentioned in this leaflet, inform your doctor or pharmacist.

5. STORING OMEPRAZOLE CAPSULES

Do not store above 30°C. Store in the original package.

Keep the bottle tightly closed.

Keep out of the reach and sight of children.

Expiry date:

Imprinted on each package.

Do not use Omeprazole 10mg, 20mg and 40mg Capsules after the expiry date indicated on the package.

Availability:

The medicinal product is available on prescription only.

This leaflet was written in January 2005.

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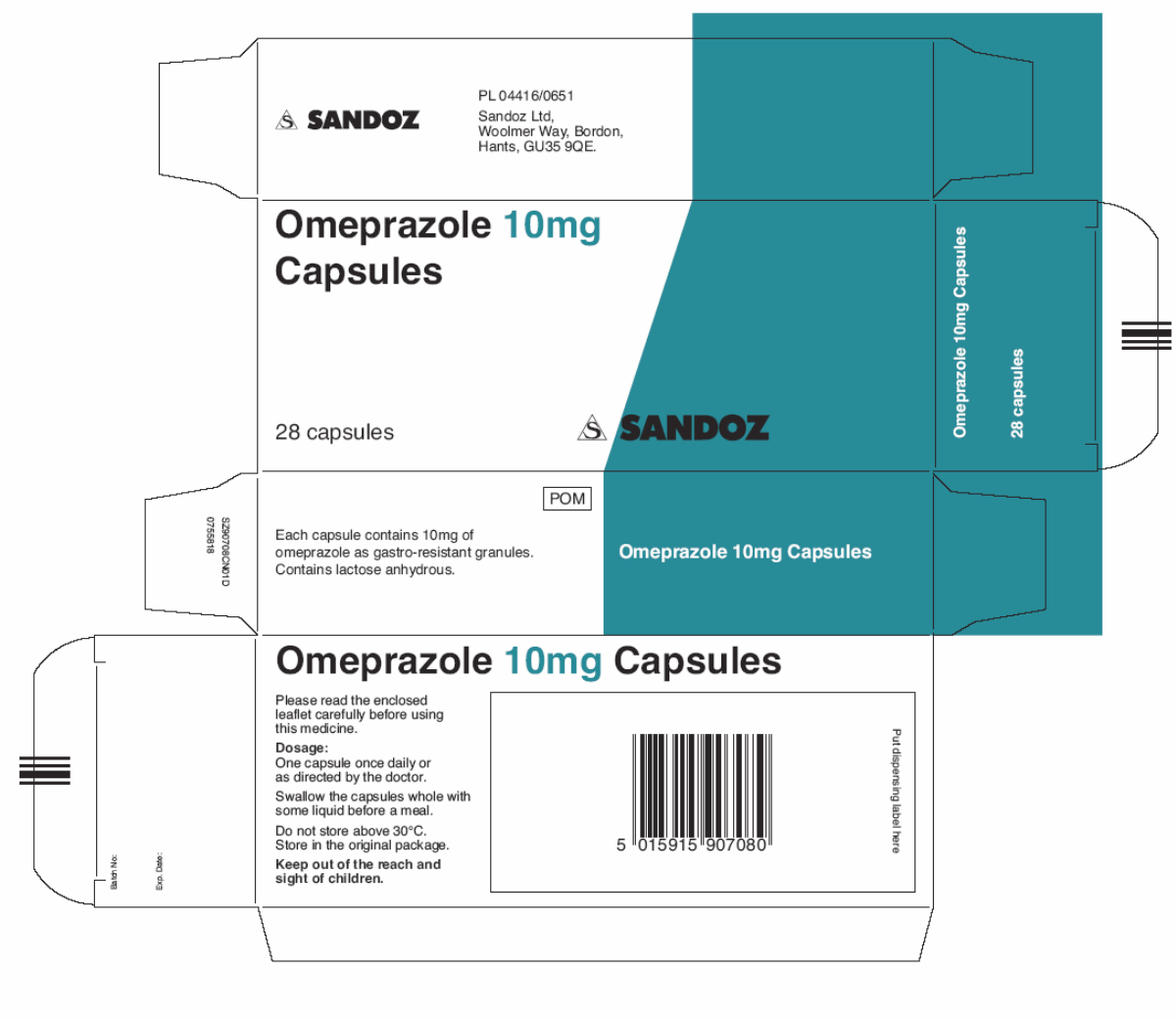
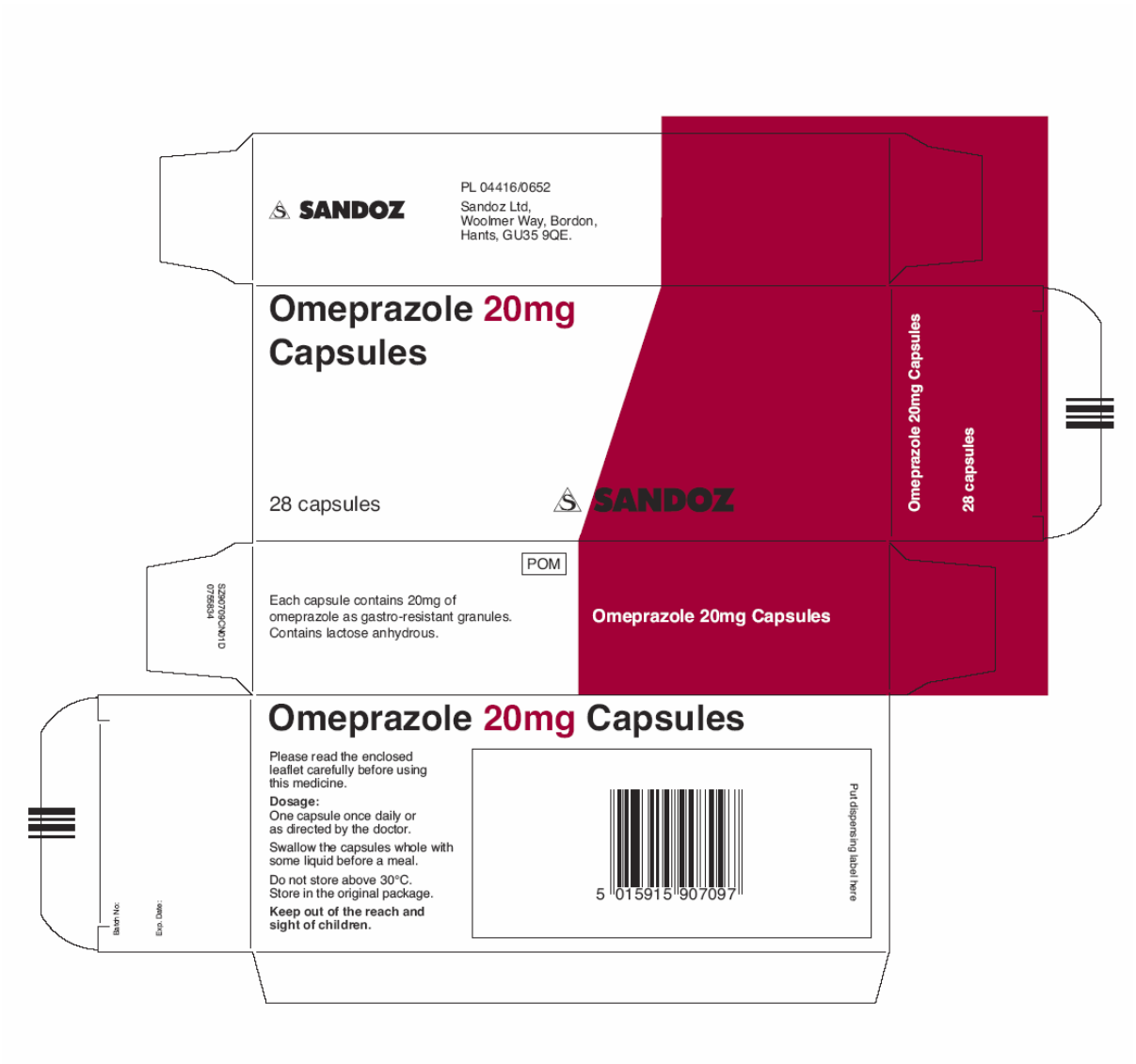
0755796

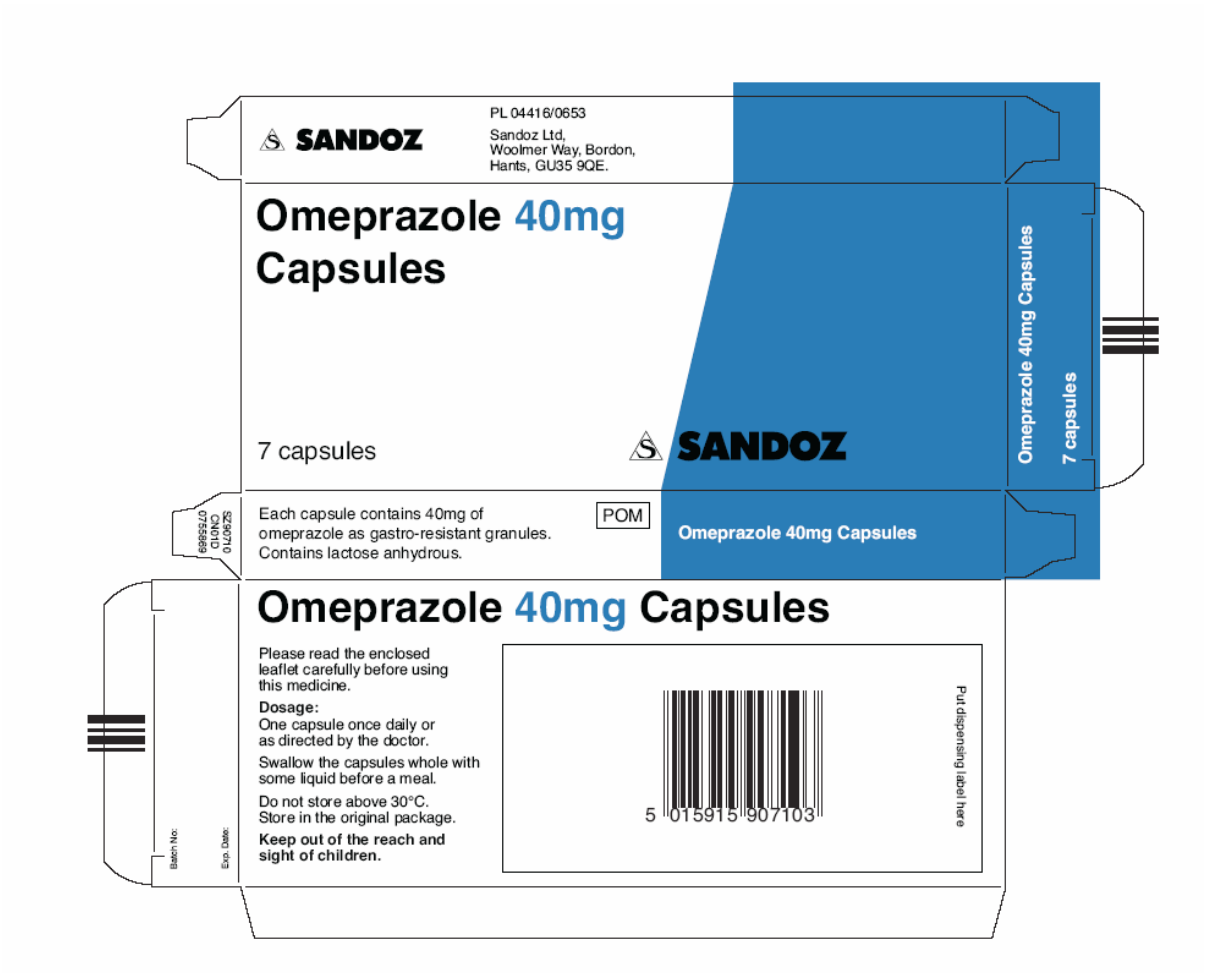
Module 4

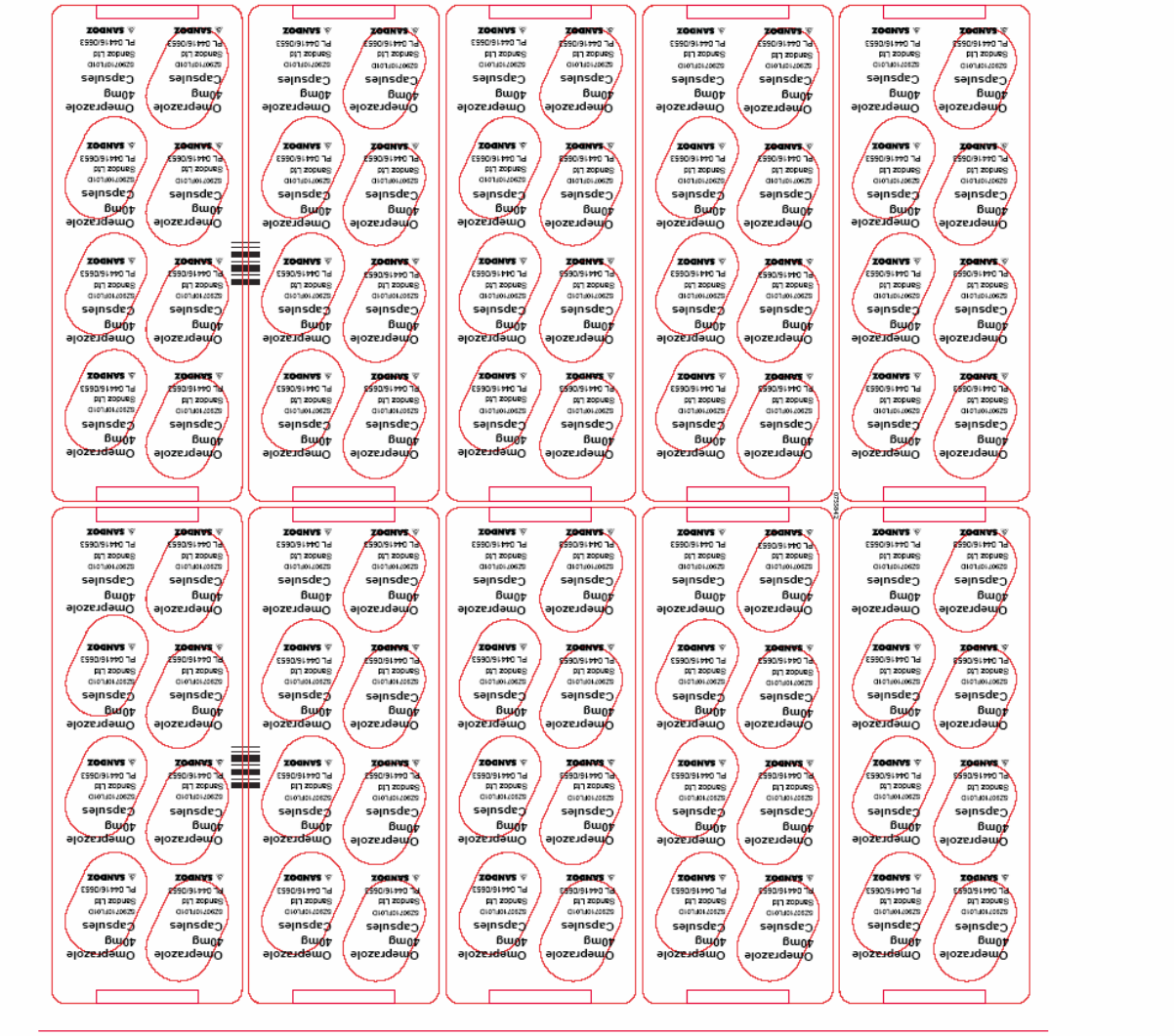
Labelling


SANDOZ
PL 04416/0651
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
Omeprazole 10mg Capsules
28 capsules
SANDOZ
POM
Each capsule contains 10mg of omeprazole as gastro-resistant granules.
Contains lactose anhydrous.
Omeprazole 10mg Capsules
Omeprazole 10mg Capsules
28 capsules
Omeprazole 10mg Capsules
Please read the enclosed leaflet carefully before using this medicine.
Dosage:
One capsule once daily or as directed by the doctor.
Swallow the capsules whole with some liquid before a meal.
Do not store above 30°C.
Store in the original package.
Keep out of the reach and sight of children.
5 015915 907080
Put dispensing label here
Batch No:
Exp. Date:


SANDOZ
PL 04416/0652
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
Omeprazole 20mg Capsules
28 capsules
SANDOZ
POM
Each capsule contains 20mg of omeprazole as gastro-resistant granules. Contains lactose anhydrous.
Omeprazole 20mg Capsules
28 capsules
Omeprazole 20mg Capsules
Please read the enclosed leaflet carefully before using this medicine.
Dosage:
One capsule once daily or as directed by the doctor.
Swallow the capsules whole with some liquid before a meal.
Do not store above 30°C.
Store in the original package.
Keep out of the reach and sight of children.
5 015915 907097
Put dispensing label here
Batch No:
Exp. Date:


Omeprazole
20mg
Capsules
SANDOZ
PL 04416/0652
Sandoz Ltd
IE290709/1010


SANDOZ
PL 04416/0653
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
Omeprazole 40mg Capsules
7 capsules
SANDOZ
Omeprazole 40mg Capsules
7 capsules
Each capsule contains 40mg of omeprazole as gastro-resistant granules.
Contains lactose anhydrous.
POM
Omeprazole 40mg Capsules
Please read the enclosed leaflet carefully before using this medicine.
Dosage:
One capsule once daily or as directed by the doctor.
Swallow the capsules whole with some liquid before a meal.
Do not store above 30°C.
Store in the original package.
Keep out of the reach and sight of children.
5 015915 907103
Put dispensing label here
Batch No:
Exp. Date:


Omeprazole
40mg
Capsules
SANDOZ

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted marketing authorisations for Omeprazole 10mg, 20mg and 40mg Capsules, from Sandoz Limited for the following:

10mg and 20mg:

- Treatment of gastrooesophageal reflux disease including reflux oesophagitis, maintenance treatment of reflux oesophagitis and treatment of symptoms associated with acid reflux disease.
- Treatment of duodenal ulcer and benign gastric ulcers including those complicating NSAID therapy.
- Treatment and maintenance treatment for relapse prevention of NSAID-related benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients who require continued NSAID treatment and have a history of gastroduodenal lesions.
- Acid-related epigastric disorders (dyspepsia).
- *Helicobacter pylori* eradication: in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.
- Prophylaxis of acid aspiration.
- Zollinger-Ellison syndrome.

40mg:

- Treatment of gastrooesophageal reflux disease including reflux oesophagitis.
- Treatment of duodenal ulcer and benign gastric ulcers including those complicating NSAID therapy.
- *Helicobacter pylori* eradication: in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.
- Prophylaxis of acid aspiration.
- Zollinger-Ellison syndrome.

These are applications made under Article 10.1 of 2001/83 EC for Omeprazole 10, 20 and 40mg Capsules, claiming essential similarity [Bioequivalence] to Mopral® 20mg Omeprazole Delayed Release Capsule (Astra Zeneca, France), which have been granted licences within the EU for over 10 years.

Omeprazole belongs to a class of substituted benzimidazoles that do not exhibit anticholinergic or H2 histamine antagonistic effects but reversibly suppress gastric acid secretion by inhibiting the enzyme H+K+-ATPase at the secretory surface of the gastric parietal cell. This enzyme system is considered as the acid (proton) pump and is responsible for the final step in gastric acid secretion. Omeprazole capsules are a controlled-release preparation.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products prior to granting their national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The products were granted marketing authorisations in the UK on 27th January 2005. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Sandoz Limited) gained approval for marketing authorisations in Austria, Belgium, Czech Republic, Estonia, Germany, Greece, Hungary, Lithuania, Luxembourg, The Netherlands, Poland, Portugal and Slovak Republic

Omeprazole 10mg, 20mg and 40mg Capsules are available on prescription.

During the procedure, potential serious risks to public health concerns were raised by two CMSs and a CMD referral was initiated:

- One CMS raised major public health objections as follows:
  i) it was felt that because of the nature of the product (gastro-resistant pellets in capsules) a multiple-dose study should be conducted (in the dossier provided, only single-dose studies were presented).
  ii) it was felt that the composition of the 40mg strength was not dose proportional to the other strengths, and a separate bioequivalence study should be conducted for this dose.
  iii) it was felt that the applicant had not fully justified their evaluation of bioequivalence and should provide additional documentation of the pharmacokinetic modelling and explorative analyses.
- Points i) and ii) were also raised by a second CMS, which felt that at least one multiple dose study should be conducted and that a separate bioequivalence study should be performed for the 40mg dose.

The CMD referral was ended positively and approval was granted by all concerned member states on the understanding that the marketing authorisation holder commits to performing additional studies.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Omeprazole 10 mg Capsules Omeprazole 20 mg Capsules Omeprazole 40 mg Capsules
Name(s) of the active substance(s) (INN)	Omeprazole
Pharmacotherapeutic classification (ATC code)	A02B C01
Pharmaceutical form and strength(s)	Capsules: 10, 20 and 40 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/799/01-03
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Estonia, Germany, Greece, Hungary, Lithuania, Luxembourg, The Netherlands, Poland, Portugal and Slovak Republic.
Name and address of manufacturer responsible for batch release in the EEA	Lek Pharmaceuticals DD, Verovskova 57, P.O.Box 81, Ljubljana, Slovenia
Date of first authorisation	27th January 2005
Marketing Authorisation Number(s)	PL 04416/0651-3
Date of assessment report	25th May 2005
Name and address of the authorisation holder	Sandoz Limited, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE

III SCIENTIFIC OVERVIEW AND DISCUSSION

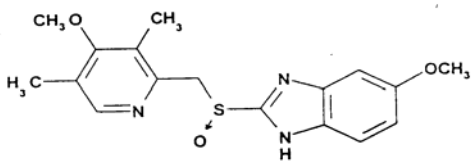
III.1 QUALITY ASPECTS

S. Active substance

Omeprazole is described in the European Pharmacopoeia, has the chemical name: (RS)-5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-1H-benzimidazole.

CAS reg. no: 73590-58-6

Structure:



Molecular formula: $C_{17}H_{19}N_3O_3S$ Molecular weight: 345.4

General properties: White or almost white powder, very slightly soluble in water, soluble in methylene chloride, sparingly soluble in alcohol and methanol. It dissolves in dilute solutions of alkali hydroxides.

The active substance specification is considered to be in compliance with the pharmacopoeial monograph. The analytical methods used for quality control of omeprazole are appropriately described and validated. The limits for residual solvents proposed by the AIMs are within the ICH guideline (CPMP/ICH/283/95) and are satisfactory. Satisfactory batch analysis data have been provided to show compliance with the proposed specification.

The packaging used to store active omeprazole is suitable for use and complies with relevant guidelines concerning contact of materials with foodstuff. Satisfactory stability data have been provided by both active substance manufacturers showing that a retest period of 24 months for one manufacturer and a retest period of 4 years when stored at 2-8°C is appropriate for this substance. The active substance manufacturer with a 24-month retest period has committed to continuing their stability studies to 5 years and placing at least one production-scale batch of active substance per year on stability studies.

P Medicinal Product

P.1 Composition

Composition

Omeprazole Capsule compositions contain the active substance omeprazole (Ph Eur) with the excipients low-substituted hydroxypropyl cellulose (NF), microcrystalline cellulose (Ph Eur), lactose anhydrous (Ph Eur), croscarmellose sodium (Ph Eur), povidone (Ph Eur), polysorbate 80 (Ph Eur), hypromellose phthalate (Ph Eur), dibutyl sebacate (NF), talc (Ph Eur), anhydrous ethanol (Ph Eur) and acetone (Ph Eur). Capsule shell ingredients are carrageenan, potassium chloride, titanium dioxide, yellow iron oxide, red iron oxide, hypromellose and water. Printing ink ingredients consist of shellac, ethyl alcohol, isopropyl alcohol, propylene glycol, N-butyl alcohol, ammonium hydroxide, potassium hydroxide, purified water and black iron oxide.

Container/closure system

Capsules are packed in aluminium/aluminium blisters (pack sizes of 7, 14, 15, 28, 30, 56, 56x1 [10mg and 20mg only] and 98), desiccated HDPE bottles with polypropylene cap (pack sizes of 30 [all strengths] and 100 [20mg only]), and desiccated amber glass bottles with screw cap closures (pack sizes of 15).

The sources and specifications of containers and blister forming materials are specified and supported by certificates of analysis. Materials are tested routinely before use. All materials comply with EU regulations regarding suitability for contact with food (90/128/EC).

P.2 Pharmaceutical development

The objective of the development programme was to develop a globally acceptable, stable and bioequivalent tablet dosage form of omeprazole comparable to Mopral® 20mg Omeprazole delay-release capsules (Astra Zeneca, France).

Conventional excipients are used at typical levels for a product of this type. The function of each ingredient included in the product has been described, and a satisfactory summary of excipient-active compatibility studies has been provided. The results showed compatibility with all of the ingredients included in the products. Levels of excipients have been selected on the basis of optimisation studies.

A copy of the formulation development report has been provided. This is satisfactory.

Omeprazole is sensitive to light, temperature, water and humidity, organic solvents and exposure to acid, but relatively stable under alkaline conditions. Degradation is often accompanied by a violet to black discoloration.

Comparative dissolution profiles for each strength of the generic and brand leader capsules have been provided, showing a comparable dissolution rate between products.

Comparative impurity profiles of the brand leader and generic capsules demonstrated chemical essential similarity, with both products showing a similar impurity profile.

P.3 Method of preparation of the product

The method of manufacture is satisfactory. A satisfactory flow chart of the manufacturing process has been provided.

In-process controls applied include loss of drying at four stages of manufacture, colour and appearance of capsule and contents, length and weight variation, and water content. Satisfactory tests and acceptance criteria have been established for in-process testing.

Process validation

The manufacturing process has been suitably validated for batches of each strength of capsule. Validation protocols have been supplied for all manufacturers and are acceptable. The applicant has committed to fully validating the first commercial-scale batches produced.

P.4 Control of other substance(s) (excipients)

All ingredients comply with relevant Ph Eur monographs with the exception low-substituted hydroxypropyl cellulose and dibutyl sebacate that, in the absence of Ph Eur monographs, are controlled to the NF. Satisfactory certificates of analysis have been provided for all excipients and capsule shells.

With the exception of lactose anhydrous, all excipients are derived from non-animal sources. Lactose anhydrous is derived from milk sourced from healthy animals under the same conditions as that collected for human consumption.

P.5 Control tests on the finished product

Finished Product Specification

Tests
Colour and appearance of capsules
Colour and appearance of content
Mass
Uniformity of mass
Water
Identification
Assay (omeprazole)
Dissolution: Acid phase Buffer phase
Related substances/degradation products
Residual solvents
Microbial quality

The applicant has provided adequate justifications for the finished product specification. Satisfactory analytical methods have been provided.

Batch Analysis

Batch analysis data from two batches of each capsule strength have been provided. All data demonstrate compliance with the finished product specification.

P.6 Packaging Materials

Satisfactory specifications and Certificates of Analysis have been provided for packaging materials, which conform with the Ph Eur. The finished product manufacturer performs satisfactory tests, as appropriate, on receipt of the packaging components.

P.7 Stability tests on the finished product

Stability data has been generated for two process validation batches of each strength of finished product stored in the packaging proposed for marketing. Testing was performed at 25°C/60%RH for 24 months, 30°C/60%RH for up to 12 months and 40°C/75% RH for up to 6 months. Analytical methods were the same as those described for product at release.

In-use stability data were also provided for finished product stored in the HDPE bottle packaging.

The stability data provided supports a shelf life of 24 months with the storage conditions “Do not store above 30°C. Store in the original package. Keep the bottle tightly closed”. The results of the in-use stability test supports the conclusion that capsules are stable for at least 100 days after first opening. Given the inclusion of dessicant in the bottles, it is accepted that no in-use shelf life is necessary.

Satisfactory commitments have been provided relating to current and future stability batches.

Conclusion on quality
The pharmaceutical assessor concluded that marketing authorisations may be granted for these products.

III.2 PRE-CLINICAL ASPECTS
These are applications made under Article 10.1 of 2001/83 EC for Omeprazole 10, 20 and 40mg Capsules, claiming essential similarity [Bioequivalence] to Mopral® 20mg Omeprazole Delayed Release Capsule (Astra Zeneca, France), which have been granted licences within the EU for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report (author: Predrag Sikiric, M.D., Ph. D., Professor) summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology
The applicant has conducted a single-dose comparative bioavailability study of test product 20mg capsules versus Mopral® 20mg Omeprazole Delayed-Release Capsule under fasted conditions.

The design was open-label randomised single-dose three-period crossover in 30 healthy male volunteers and six alternates. Results were as follows:

Table 1

	Omeprazole Lec *v* Omeprazole Astra **Ratio least squares** **90% CI**
AUC_{0-t}	94.1 87.8-100
AUC_{0-inf}	95.1 88.8-101.95
C_{max}	92.8 82.6 - 104.3

Additionally, the applicant has conducted a second single-dose bioavailability study of the test product 20mg capsules versus Mopral® 20mg Omeprazole Delayed-Release Capsule under fed conditions.

The design was open-label randomised single-dose three-period crossover in 30 healthy male volunteers and six alternates. Results were as follows:

Table 2

	Omeprazole Lec *v* Omeprazole Astra **Ratio least squares** **90% CI**
AUC_{0-t}	93.2 86.6-100.2
AUC_{0-inf}	93.3 86.2-101.0
C_{max}	104.9 92.5-118.9

III.3.2 Clinical Efficacy
No new data.

III.3.3 Clinical Safety
No new data.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The applicant has demonstrated comparable bioavailability between test and reference products under fasted and fed conditions. Marketing authorisations may be granted for these products.