OMEPRAZOLE 20 MG GASTRO-RESISTANT CAPSULES

PL 08608/0135

UKPAR

TABLE OF CONTENTS

OMEPRAZOLE 20 MG GASTRO-RESISTANT CAPSULES

PL 08608/0135

LAY SUMMARY

The MHRA granted Olinka UK Limited a Marketing Authorisation (licence) for the medicinal product Omeprazole 20 mg Gastro-resistant Capsules on 12 September 2008. This product, to be available by prescription only (POM), contains omeprazole and is used for the following:

1. Treatment of reflux oesophagitis disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid.
2. Treatment of duodenal and benign gastric ulcers including complicating NSAID therapy.
3. Relief of reflux-like symptoms (e.g. heartburn) and/or ulcer-like symptoms (e.g. epigastric pain) associated with acid-related dyspepsia.
4. Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment.
5. Relief of associated dyspeptic symptoms.
6. *Helicobacter pylori* eradication: When used with in combination with antibiotics, Omeprazole proves effective in the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.
7. Prophylaxis of acid aspiration.
8. Zollinger-Ellison syndrome.

The active ingredient omeprazole is a type of drug called a proton-pump inhibitor. It reduces the production of acid in your stomach.

This application cross-refers to Omeprazole 20mg Gastro-resistant Capsules (PL 24577/0004) licensed to Laboratorios DAVUR.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Omeprazole 20 mg Gastro-resistant Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

OMEPRAZOLE 20 MG GASTRO-RESISTANT CAPSULES

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SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Omeprazole 20 mg Gastro-resistant Capsules to Olinka UK Limited on 12 September 2008. The product is available as a prescription-only medicine (POM).

The application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Omeprazole 20mg Gastro-resistant Capsules (PL 24577/0004) licensed to Laboratorios DAVUR.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report was generated for it.

The active ingredient 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 20mg Gastro-resistant Capsules is indicated for the following:
1. Treatment of reflux oesophagitis disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid.
2. Treatment of duodenal and benign gastric ulcers including complicating NSAID therapy.
3. Relief of reflux-like symptoms (e.g. heartburn) and/or ulcer-like symptoms (e.g. epigastric pain) associated with acid-related dyspepsia.
4. Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment.
5. Relief of associated dyspeptic symptoms.
6. *Helicobacter pylori* eradication: When used with in combination with antibiotics, Omeprazole proves effective in the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.
7. Prophylaxis of acid aspiration.
8. Zollinger-Ellison syndrome.

PHARMACEUTICAL ASSESSMENT

Introduction

This is a simple application for Omeprazole 20 mg Gastro-resistant Capsules submitted under Article 10c of EC Directive 2001/83 as amended, cross-referencing Omeprazole 20mg Gastro-resistant Capsules (PL 24577/0004) licensed to Laboratorios DAVUR. The cross-referenced product was licensed to Rockspring Healthcare Ltd on 5 May 2005 but then underwent a change of ownership to Laboratorios DAVUR S.L on 13 September 2005. A satisfactory letter of consent has been provided by the license holder of the cross referenced product.

Product name

The proposed product name is the generic name and therefore is acceptable.

Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains omeprazole, equivalent to 20 mg. It is to be stored in either a HDPE bottle with polypropylene cap with integral silica gel dessicant or an HDPE bottle with child-resistant polypropylene cap with integral silica gel dessicant. Each pack contains 28 capsules.

Therapeutic indications

This product can be used for the following:

1. Treatment of reflux oesophagitis disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid.
2. Treatment of duodenal and benign gastric ulcers including complicating NSAID therapy.
3. Relief of reflux-like symptoms (e.g. heartburn) and/or ulcer-like symptoms (e.g. epigastric pain) associated with acid-related dyspepsia.
4. Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment.
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7. Prophylaxis of acid aspiration.
8. Zollinger-Ellison syndrome.

Legal status

This product is available as a prescription-only medicine (POM).

Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

Finished product
The proposed finished product specification is in-line with the details registered for the cross-reference product.

Expert report
Complete quality, preclinical and clinical summaries have been provided. Expert statements in relation to the quality, clinical and non-clinical aspects of the product confirming that they are identical to the cross-reference product are provided by suitably qualified persons.

Summary of Product Characteristics
The proposed summary is consistent with the details registered for the cross-reference product.

Patient Information Leaflet
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. The applicants refer to the user test submitted with the cross reference product.

Label
These are consistent with the cross-reference product.

Assessor's Overall Conclusions
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

As this is a duplicate application, no new preclinical data have been supplied and none are required.

CLINICAL ASSESSMENT

As this is a duplicate application, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

QUALITY
The data for this application are consistent with that previously assessed for the cross-reference product and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
The efficacy of omeprazole is well known.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

BENEFIT: RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the compound. The benefit: risk is, therefore, considered to be positive.

OMEPRAZOLE 20MG GASTRO-RESISTANT CAPSULES

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 8 May 2008.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12 May 2008.
3	Following assessment of the application the MHRA requested further information on 30 June 2008.
4	The applicant responded to the MHRA's requests, providing further information on 21 August 2008.
5	Following assessment of the response the MHRA requested further information on 21 August 2008.
6	The applicant responded to the MHRA's requests, providing further information on 8 September 2008.
7	The application was determined on 12 September 2008.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Omeprazole 20 mg Gastro-resistant Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains omeprazole 20 mg.
Also contains sucrose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant Capsules, hard
Each capsule consists of an orange body and blue cap and contains white to beige granules marked with O20.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Treatment of reflux oesophagitis disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid.

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

3. Relief of reflux-like symptoms (e.g. heartburn) and/or ulcer-like symptoms (e.g. epigastric pain) associated with acid-related dyspepsia.

4. Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment.

5. Relief of associated dyspeptic symptoms.

6. *Helicobacter pylori* eradication: When used with in combination with antibiotics, Omeprazole proves effective in the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.

7. Prophylaxis of acid aspiration.

8. Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Oesophageal reflux disease including reflux oesophagitis:

The usual starting dose is 20 mg omeprazole taken once a day for 4 weeks. For those patients not fully healed after the initial 4 week course, healing usually occurs during a further 4-8 weeks treatment.

Omeprazole has also been used in a dose of 40mg once a day in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks. Continuation of therapy can be considered at a dosage of 20 mg once daily.

Acid reflux disease:
For long-term management, a dose of 10 mg once daily is recommended, increasing to 20 mg if symptoms return.

Duodenal and benign gastric ulcers:
The usual dose is 20 mg omeprazole once daily. With duodenal ulcers, the majority of patients usually are healed after 4 weeks of treatment. The majority of patients with benign gastric ulcer are healed after 8 weeks. In severe or recurrent cases the dose may be increased to 40 mg omeprazole daily. For patients with a history of recurrent duodenal ulcer, long term therapy is recommended at a dosage of 20 mg omeprazole once daily.

To prevent recurrence, in patients with duodenal ulcer, the recommended dose is omeprazole 10 mg, once daily, increasing to 20 mg, once daily if symptoms return.

The following groups of patients are at risk from recurrent ulcer relapse: those with *Helicobacter pylori* infection, younger patients (<60 years), those whose symptoms persist for more than one year and smokers. These patients will require initial long-term therapy with omeprazole 20 mg once daily, reducing to 10 mg once daily, if necessary.

Acid-related dyspepsia:
Usual dosage is 10 mg or 20 mg omeprazole once daily for 2 – 4 weeks depending on the severity and persistence of symptoms.

If the patient does not respond to treatment after 4 weeks or who relapse shortly after treatment, then the patient should be investigated.

For the treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions:
The recommended dosage of omeprazole is 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment.

For the prophylaxis of NSAID-associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment:
The recommended dosage is 20 mg omeprazole taken once a day.

***Helicobacter pylori (Hp)* eradication regimens in peptic ulcer disease:**
Omeprazole is recommended at a dose of 40 mg once daily or 20 mg twice daily concomitant with antimicrobial agents as detailed below:

Triple therapy regimens in duodenal ulcer disease:
Omeprazole and the following antimicrobial combinations;

Amoxicillin 500 mg and metronidazole 400 mg both three times a day for one week.
or
Clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice a day for one week.

or
Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week.

Dual therapy regimens in duodenal ulcer disease
Omeprazole and amoxicillin 750 mg to 1 g twice daily for two weeks. Alternatively, omeprazole and clarithromycin 500 mg three times a day for two weeks.

Dual therapy regimens in gastric ulcer disease:
Omeprazole and amoxicillin 750 mg to 1 g twice daily for two weeks.

In each regimen if symptoms return and the patient tests positive for *Hp*, therapy may be repeated or one of the alternative regimens can be used; if the patient is *Hp* negative then see dosage instructions for acid reflux disease.
To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for duodenal and benign gastric ulcer.

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

Zollinger-Ellison syndrome:
The initial starting dose is omeprazole 60 mg once a day. The dosage should be adjusted individually and treatment continued as long as clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20 – 120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Elderly:
Dose adjustment is not required in the elderly.

Children
Reflux oesophagitis
The treatment time is 4–8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux Disease
The treatment time is 2-4 weeks. If symptom control has not been achieved after 2-4 weeks the patient should be investigated further.

The dosage recommendations are as follows:

Age	**Weight**	**Dosage**
≥ 1 year of age 1 The dosage can be increased to 20 mg once daily if needed.	0-20 kg 10 mg	once daily.
≥ 2 years of age The dosage can be increased to 40 mg once daily if needed.	> 20 kg 20 mg	once daily.

Children over 4 years of age

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori. When selecting appropriate combination therapy consideration should be given to official local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

Weight	**Dosage**
15-≤30 kg	Combination with two antibiotics: Omeprazole 10 mg, amoxicillin 25mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together 2 times daily for 1 week
30-≤40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered 2 times daily for 1 week.
>40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered 2 times daily for 1 week.

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

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

For patients (including children aged 1 year and above who can drink or swallow semi-solid food) who are unable to swallow omeprazole Capsules:

The capsules may be opened and the contents swallowed directly with half a glass of water or suspended in 10 ml of non-carbonated water, any fruit juice with a pH less than 5 e.g. apple, orange, pineapple, or in applesauce or yoghurt and swallowed after gentle mixing. The dispersion should be taken immediately or within 30 minutes. Stir just before drinking and rinse it down with half a glass of water. Alternatively the actual capsules may be sucked and then swallowed with half a glass of water. There is no evidence to support the use of sodium bicarbonate buffer as a delivery form. It is important that the contents of the capsules should not be crushed or chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
When gastric ulcer is suspected, the possibility of malignancy should be excluded before treatment with Omeprazole 20 mg Capsules is commenced, as treatment may alleviate symptoms and delay diagnosis.

Omeprazole like other proton pump inhibitors should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

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 a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

This product contains sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Some children with chronic illnesses may require long-term treatment although it is not recommended'.

4.5 Interaction with other medicinal products and other forms of interaction

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

As omeprazole is metabolised in the liver through cytochrome P450, it can prolong the elimination of diazepam, phenytoin, warfarin and other vitamin K antagonists which are in part substrates for this enzyme. Monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be required. However, concomitant treatment with Omeprazole 20 mg once daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. Similarly, concomitant treatment with Omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication. There is no interaction with metronidazole or amoxicillin. These antimicrobials are used concomitantly with omeprazole for the eradication of *H. pylori*.

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, ciclosporin, lidocaine, quinidine, estradiol, or antacids. The absorption of Omeprazole 20 mg Capsules is not affected by alcohol or food.
There is no evidence of an interaction with piroxicam, diclofenac or naproxen. This is considered useful when patients are required to continue these treatments.

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

Co-administration of omeprazole (40mg once daily) with atazanavir 300 mg/ritonavir 100mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax, and Cmin). Increasing the atazanavir dose to 400mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including omeprazole should not be co-administered with atazanavir (see section 4.3).
Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.
Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUCτ by 15% and 41%, respectively. A dose adjustment of omeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

4.6 Pregnancy and lactation

Well-conducted epidemiological studies indicate no adverse effects of Omeprazole 20 mg on pregnancy or on the health of the foetus/new-born child. Omeprazole 20 mg can be used during pregnancy.

Omeprazole is excreted into breast milk but is unlikely to influence the child when used in therapeutic doses.

4.7 Effects on ability to drive and use machines

Omeprazole 20 mg Gastro-resistant Capsules has negligible influence on the ability to drive and use machines.

However if side effects such as dizziness and light headedness are experienced the ability to drive and use machines may be affected (see section 4.8).

4.8 Undesirable effects

Omeprazole 20 mg Capsules are well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use but in many cases a relationship to treatment with omeprazole has not been established.
The following definitions of frequencies are used:

Common ≥ 1/100 to <1/10
Uncommon ≥ 1/1000 to < 1/100
Rare ≥ 1/10, 000 to <1/1000

	Common	**Uncommon**	**Rare**
Nervous system disorders:	Headache	Dizziness, paraesthesia, light headedness, feeling faint, somnolence, insomnia and vertigo	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
Gastrointestinal disorders:	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence		Dry mouth, stomatitis and gastrointestinal candidiasis
Hepatobiliary disorders:		Increased liver enzymes	Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure
Skin and subcutaneous tissue disorders:		Rash and/or pruritus Urticaria	Photosensitivity, bullous eruption erythema multiforme, Stevens-Johnson syndrome, toxic

			epidermal necrolysis (TEN), alopecia
Endocrine disorders			Gynaecomastia
Blood and lymphatic system disorders:			Leukopenia, thrombocytopenia, Agranulocytosis and pancytopenia
Musculoskeletal and connective tissue disorders:			Arthritic and myalgic symptoms and muscular weakness
Reproductive system and breast disorders:			Impotence
General disorders and administration site conditions:		Malaise	Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

4.9 Overdose

Rare reports have been received of overdosage with omeprazole. Doses of up to 560 mg have been described and occasional reports have been received when single oral doses have been reached up to 2400 mg, which is 120 times the recommended clinical dose. Overdosage of omeprazole is reported to be associated with nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache. Single cases of apathy, depression and confusion have been described.

The symptoms described in connection with omeprazole overdosage have been transient and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment is needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A02B C01 - Drugs for peptic ulcers and gastro-oesophageal reflux disease (GORD) - Proton Pump inhibitors.

Omeprazole reduces gastric acid secretion through a unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible inhibition of gastric acid secretion with once daily dosing.

An oral dose of 20 mg once a day produces a rapid and effective inhibition of gastric acid secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80% in 24-hour intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70%, twenty-four hours after dosing with Omeprazole 20 mg Capsules.

Clinical data for omeprazole in the prophylaxis of NSAID induced gastroduodenal lesions are derived from clinical studies of up to 6 months duration.

Helicobacter pylori (*Hp*) is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with this bacterium. *Hp* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *Hp* and gastric carcinoma.

Omeprazole has been shown to have a bactericidal effect on *Hp* in vitro.

Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

In recent clinical data in patients with acute peptic ulcer omeprazole *Hp* eradication therapy improved patients' quality of life.

During long-term treatment an increased frequency of gastric glandular cysts has been reported. These changes are a physiological consequence of pronounced inhibition of acid secretion. The cysts are benign and appear to be reversible. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

Paediatric data
In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0-24 months with clinically diagnosed GERD were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50 % after 8 weeks of treatment irrespective of the dose.
Eradication of Helicobacter pylori in children:
A randomised, double blind clinical study (Héliot study) has concluded to the efficacy and an acceptable safety for omeprazole associated to two antibiotics (amoxicillin and clarithromycin) in the treatment of Helicobacter pylori infection in children of 4 years old and above with a gastritis: Helicobacter pylori eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

Site and mechanism of action

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

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

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole is acid labile and is administered orally as enteric-coated granules in capsules. Absorption takes place in the small intestine and is usually completed within 3 – 6 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

Elimination and metabolism

The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at a given time.

Omeprazole is entirely metabolised, mainly in the liver. Identified metabolites in plasma are the sulfone, the sulfide 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.

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function. 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

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise Omeprazole.

5.3 Preclinical safety data

Animal toxicity:

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any individual drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres

Sodium starch glycolate
Sodium laurilsulfate
Povidone
Potassium oleate
Oleic Acid
Hypromellose
Methacrylic acid - ethyl acrylate (1:1)
Triethyl citrate
Titanium dioxide
Talc

Capsule
Gelatin
Titanium dioxide (E171)
Quinoline yellow (E104)
Indigo carmine (E132)
Erythrosine (E127)

Printing Ink
Shellac
Polyvinylpyrrolidone
Propylene glycol
Sodium Hydroxide
Titanium Dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
HDPE bottle and polypropylene cap with integral silica gel dessicant.
HDPE bottle and child-resistant polypropylene cap with integral silica gel dessicant.

Each pack contains 28 capsules.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Olinka (UK) Limited
38/40 Chamberlayne Road
London
United Kingdom
NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)

PL 08608/0135

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/09/2008

10 DATE OF REVISION OF THE TEXT

12/09/2008

PATIENT INFRORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
OMEPRAZOLE 20 mg GASTRO-RESISTANT CAPSULES
(Omeprazole)

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

In this leaflet:

1. WHAT OMEPRAZOLE GASTRO-RESISTANT CAPSULES ARE AND WHAT THEY ARE USED FOR

The active ingredient, omeprazole, belongs to a group of medicines called "proton pump inhibitors". It works by reducing the production of acid in your stomach.

Omeprazole is used to treat the following conditions:
- Reflux oesophagitis and Oesophageal reflux disease, where acid from the stomach escapes into the food pipe causing pain, inflammation and heartburn.
- Acid indigestion (dyspepsia) which can cause stomach pain and/or discomfort.
- Ulcers in the upper part of the intestine (duodenal ulcer) or stomach (gastric ulcer). For patients who have had previous trouble with an ulcer and need to continue therapy with a non-steroidal anti-inflammatory drug (NSAID), omeprazole can heal ulcers or prevent an ulcer developing. In such patients, omeprazole protects the stomach or duodenum whilst they are taking NSAIDs.
- Ulcers which are infected with bacteria called *Helicobacter pylori.*
- Prevention of damage to the lungs caused by breathing in stomach fluids (acid aspiration), e.g. before an operation.
- *Zollinger-Ellison syndrome,* when excess stomach acids are produced due to a growth in the pancreas.

2. BEFORE YOU TAKE OMEPRAZOLE GASTRO-RESISTANT CAPSULES

If any of the following applies to you, speak to your doctor or pharmacist before taking Omeprazole Capsules as they may not be suitable for you.

Do not take Omeprazole Capsules:
- if you are hypersensitive (allergic) to omeprazole or any of the other ingredients of Omeprazole Capsules.
- if you are taking atazanavir (a medicine used to treat HIV)
- if your doctor suspects you have an ulcer, he may wish to run tests to exclude the possibility of serious illness before you take Omeprazole Capsules.

Take special care with Omeprazole Capsules:
Tell your doctor if you suffer from any of the following:
- liver problems
- if you are going to have an operation and anaesthetic (including at the dentist) tell your doctor or dentist that you are taking Omeprazole Capsules
- if you have an intolerance to sucrose

Omeprazole acts to reduce the acid in your stomach and this may lead to a slightly increased risk of infections of the stomach and intestine, such as Salmonella and Campylobacter.
Long term treatment with Omerpazole in children is not recommended. You should speak with your doctor or pharmacist if you are not sure.

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.
Check with your doctor or pharmacist, before starting treatment with Omeprazole Capsules, if you are taking any other medicines, especially the following,
- Diazepam (for your nerves)
- Phenytoin (for epilepsy)
- Warfarin and other medicines used for thinning the blood
- Digoxin (for the heart)
- Ketoconazole, itraconazole or variconazole (for fungal infections)
- Atanzanavir (for treating HIV)
- Clarithromycin (an antibiotic)
- Tacrolimus (an immunosuppressant).

Taking Omeprazole Capsules with food and drink
You can take your capsules with food or on an empty stomach at any time of the day. The capsules should not be chewed or crushed. Please refer to section 3 – How to take Omeprazole.

Pregnancy and Breast-feeding:
Omeprazole Capsules can be used during pregnancy and if you are breast-feeding.

Driving and using machines:
Your medicine does not usually affect your ability to drive or operate machinery. However you should not drive or operate machinery if you experience any side effects such as dizziness and light headedness as your ability to drive or operate machines may be affected.

Important information about some of the ingredients of Omeprazole Capsules:
This medicine contains sucrose. 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 GASTRO-RESISTANT CAPSULES

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

Omeprazole capsules should not be chewed or crushed. They should be swallowed whole with a drink of water. If you have trouble swallowing, the capsules can be opened and the contents taken in the following way:
- swallow directly with half a glass of water, or
- suspended in 10 ml of still water or fruit juice like apple, orange or pineapple, or
- gently mixed in yoghurt or apple sauce.

It is important that the contents of the capsules are not crushed or chewed and that you drink half a glass of water after you have taken the contents of the capsules.

ADULTS
Treatment for heartburn (Reflux oesophagitis and oesophageal reflux disease) - The usual dose is 20 mg omeprazole taken once a day for 4 weeks. Your doctor may ask you to continue taking the capsules or increase the dose depending on how you respond to treatment. To stop your symptoms returning your doctor may tell you to continue to take 20 mg Omeprazole or reduce the dose to 10mg.

Relief of Acid Indigestion (Dyspepsia) - The usual dose is 10 mg or 20 mg once a day for a period of 2 - 4 weeks. Your doctor will tell you how long to take your capsules for. If you do not experience any improvement in your symptoms you should return to your doctor.

Treatment of ulcers in the upper part of the intestine (duodenal ulcer) and stomach (gastric ulcer) - The usual dose is 20 mg omeprazole once a day for a period of 4 - 8 weeks depending on your symptoms. Your doctor may increase the dose depending on how you respond to treatment. To stop your ulcer coming back, the usual dose is omeprazole 10 mg once daily unless your symptoms return. If your symptoms return, your doctor may increase the dose.

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

Treatment of Ulcers caused by infection with the bacteria called *Helicobacter Pylori*
The usual dose is omeprazole 40 mg once a day or 20 mg taken twice a day for a period of 1 - 2 weeks. Your doctor will also tell you to take one or two of the following antibiotics; amoxicillin, clarithromycin, metronidazole or tinidazole. Follow the directions for taking your medicine very carefully and if you are unsure about anything, ask your doctor or pharmacist.

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

Zollinger - Ellison Syndrome - The usual starting dose is omeprazole 60 mg once a day. If the dose is more than 80 mg a day, half the dose should be taken in the morning and half at night. Your doctor will tell you how many capsules to take and when to take them.

CHILDREN
Reflux oesphagitis – The usual starting dose is dependent on age and weight. Your doctor will tell you what dose to take. Treatment should be given for 4-8 weeks. If symptoms persist after the end of the treatment consult your doctor.

Gastroesophageal reflux disease (heartburn and acid reflux) - The usual starting dose is dependent on age and weight. Your doctor will tell you what dose to take. Treatment should be given for 2-4 weeks. If symptoms persist after the end of the treatment consult your doctor.

Treatment of Ulcers caused by infection with the bacteria called *Helicobacter Pylori* - For children over the age of 4 years the dose of omeprazole and combined antibiotics will depend on their weight. Your doctor will tell you what dose to take. Treatment usually lasts 1 week but your doctor may increase this to two weeks if required.

If you take more Omeprazole Capsules than you should:
If you (or someone else) accidentally take too many Omeprazole 20 mg Capsules, contact your doctor or pharmacist immediately.

If you forget to take Omeprazole Capsules:
If you forget to take a dose, take it as soon as you remember. If it is nearly time for your next dose just take the next dose and forget about the one you missed. Do not take a double dose to make up for forgotten dose.

If you stop taking Omeprazole:
Do not stop taking Omeprazole without talking to your doctor first. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Omeprazole can cause side effects, although not everybody will experience them. These are usually mild and go away when you stop taking this medicine.

If the following happens, stop taking the capsules and tell your doctor immediately or go to the emergency department at your nearest hospital:
- An allergic reaction (angioedema): swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing.

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

Common (occur in more than 1 in 100 patients, but less than 1 in 10 patients)
- Headache
- Diarrhoea, constipation, stomach pain, sickness, feeling sick and flatulence (wind).

Uncommon (occur in more than 1 in 1000 patients but less than 1 in 100 patients)
- Dizziness or a feeling of spinning, pins and needles, light headedness, feeling faint, drowsiness and insomnia
- Increased liver enzymes
- Itchy skin, rash and hives
- Feeling of general discomfort

Rare (occur in more than 1 in 10000 but less than 1 in 1000 patients)
- Feeling of confusion, agitation, aggression, depression and hallucination
- Dry mouth, swelling of the mouth and yeast infections in the stomach or intestine
- Liver problems, jaundice (yellowing of the skin or eyes), liver failure
- Sensitivity to light, blistering, unusual reddening of the skin, flu like symptoms and blistering or skin lesions (Stevens-Johnson syndrome), patches of dead skin and hair loss
- Larger breasts (males only)
- Leukopenia, thrombocytopenia and agranulocytosis (decrease in number of blood cells)
- Arthritic symptoms, muscle pain and muscular weakness
- Impotence
- Hypersensitivity reactions e.g. rapid swelling of the skin and tissues, fever, difficulty in breathing, interstitial nephritis (kidney disease) and anaphylactic shock (strong allergic reaction). Increased sweating, peripheral oedema (swelling of hands and feet), blurred vision, taste disturbance and low blood sodium.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE OMEPRAZOLE GASTRO-RESISTANT CAPSULES

- Keep out of the reach and sight of children.
- Do not store above 30 °C. Store in the original package. Keep the bottle tightly closed.
- Do not use Omeprazole after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

- The active substance is omeprazole and each capsule contains 20 mg of omeprazole as gastro resistant granules.

- The other ingredients are: sugar spheres, sodium starch glycolate, sodium laurilsulfate, povidone, potassium oleate, oleic acid, hypromellose, methacrylic acid - ethyl acrylate copolymer (1:1), triethyl citrate, titanium dioxide and talc. The capsule coating also contains gelatin, titanium dioxide (E171), quinoline yellow (E104), indigo carmine (E132) and erythrosine (E127). The printing ink contains shellac, polyvinylpyrrolidone, propylene glycol, sodium hydroxide and titanium dioxide (E171).

What Omeprazole 20 mg Gastro-resistant Capsules look like and the contents of the pack
The capsules have an orange body and blue cap and are marked with O20. Omeprazole 20 mg. Capsules are available in bottles of 28 capsules.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Olinka (UK) Limited, 38/40 Chamberlayne Road London, UK, NW10 3JE

Manufacturer:
Laboratorios Belmac, S.A. Poligono Industrial Malpica
calle C, 50016- Zaragoza, Spain.

This leaflet was last updated in July 2008.

For information in large print, or Braille please contact the Marketing Authorisation Holder on 0034 91 659 32 20.

LABELLING

Label:

Omeprazole 20 mg Gastro-Resistant Capsules

Omeprazole 28 capsules

Each capsule contains 20 mg omeprazole. Also contains sucrose. See leaflet for further information. Oral administration only. Swallow whole with a glass of water.

Do not chew or crush. Use as directed by your doctor. Do not store above 30ºC. Store in the original package. Keep the bottle tightly closed.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder: Olinka (UK) Limited
London NW10 3JE
United Kingdom.

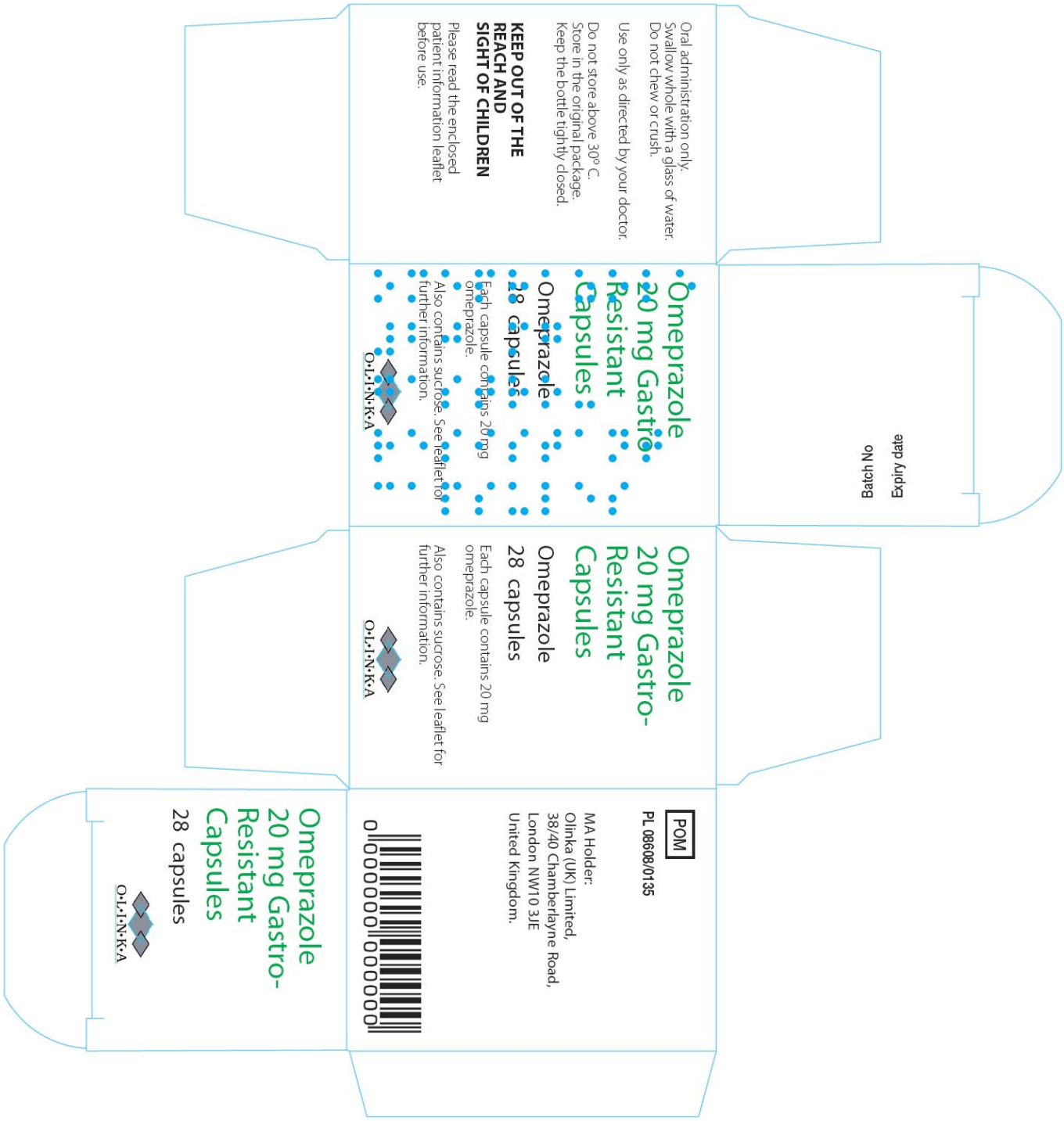
POM

PL 08608/0135

Batch no:

Expiry Date:

Carton:


Oral administration only.
Swallow whole with a glass of water.
Do not chew or crush.
Use only as directed by your doctor.
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
Please read the enclosed patient information leaflet before use.
Omeprazole 20 mg Gastro-Resistant Capsules
Omeprazole
28 capsules
Each capsule contains 20 mg omeprazole.
Also contains sucrose. See leaflet for further information.
O·L·I·N·K·A
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