

<b>Summary of Product Characteristics</b>
---

**1-NAME OF THE MEDICINAL PRODUCT (FPP)****Dafrazol®***Omeprazol***1.1. Strength** 20 mg**1.2. Pharmaceutical form** gastro-resistant capsule**2- QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 20 mg omeprazole.

Excipient with known effect: sucrose

For the full list of excipients, see section 6.1

**3- PHARMACEUTICAL FORM**

Gastro-resistant capsule

Green / yellow hard capsule containing whitish spherical gastro-resistant micro pellets

**4- CLINICAL PARTICULARS****4.1 Therapeutic indications****Adults**

- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, *Helicobacter pylori* eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux oesophagitis

- Long-term management of patients with healed reflux oesophagitis
- Treatment of symptomatic gastro-oesophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

**Children over 1 year of age and  $\geq 10$  kg**

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

**Children over 4 years of age and adolescents**

- In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*

**4.2 Posology and mode of administration****4.2.1 Posology****Adults**

- Treatment of duodenal ulcers

The recommended dose in patients with an active duodenal ulcer is Dafrazol 20 mg once daily. In most patients healing occurs within two weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further two weeks treatment period. In patients with poorly responsive duodenal ulcer 2 capsules of Dafrazol 20 mg once daily is recommended and healing is usually achieved within four weeks.

- Prevention of relapse of duodenal ulcers

For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is Dafrazol 20 mg once daily. In case of therapy failure, the dose can be increased to 2 capsules of Dafrazol 20 mg once daily.

- Treatment of gastric ulcers

The recommended dose is Dafrazol 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with poorly responsive gastric ulcer 2 capsules of Dafrazol 20 mg once daily is recommended and healing is usually achieved within eight weeks.

- Prevention of relapse of gastric ulcers

For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is Dafrazol 20 mg once daily. If needed the dose can be increased to 2 capsules of Dafrazol 20 mg once daily.

- *H. pylori* eradication in peptic ulcer disease

For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

- Dafrazol 20 mg + clarithromycin 500 mg + amoxicillin 1,000 mg, each twice daily for one week, or
- Dafrazol 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), each twice daily for one week or
- Dafrazol 2 capsules of 20 mg once daily with amoxicillin 500 mg and metronidazole 400 mg (or 500 mg or tinidazole 500 mg), both three times a day for one week.

In each regimen, if the patient is still *H. pylori* positive, therapy may be repeated.

- Treatment of NSAID-associated gastric and duodenal ulcers

For the treatment of NSAID-associated gastric and duodenal ulcers, the recommended dose is Dafrazol 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.

- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk

For the prevention of NSAID-associated gastric ulcers or duodenal ulcers in patients at risk (age > 60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding) the recommended dose is Dafrazol 20 mg once daily.

- Treatment of reflux oesophagitis

The recommended dose is Dafrazol 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with severe oesophagitis 2 capsules of Dafrazol 20 mg once daily is recommended and healing is usually achieved within eight weeks.

- Treatment of symptomatic gastro-oesophageal reflux disease

The recommended dose is Dafrazol 20 mg daily and can be increased to 2 capsules of Dafrazol 20 mg once daily in case inadequate response. If symptom control has not been achieved after four weeks treatment further investigation is recommended.

- Treatment of Zollinger-Ellison syndrome

In patients with Zollinger-Ellison syndrome the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose of omeprazole is 60 mg daily (3 capsules of Dafrazol 20 mg). All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of omeprazole 20-120 mg daily. When dose exceed 80 mg omeprazole daily, the dose should be divided and given twice daily.

#### 4.2.2 Special populations

- Renal impairment: dose adjustment is not needed in patients with impaired renal function.
- Hepatic impairment: in patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient.
- Elderly: dose adjustment is not needed in the elderly.

#### 4.2.3 Pediatric population

##### Children over 1 year of age and $\geq 10$ kg

Treatment of reflux oesophagitis

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease

The posology recommendations are as follows:

Age	Weight	Posology
$\geq 1$ year of age	10-20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed
$\geq 2$ years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed

Reflux oesophagitis: The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal 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.

#### **Children over 4 years of age and adolescents**

Treatment of duodenal ulcer caused by *H. pylori*

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.

The treatment should be supervised by a specialist.

The posology recommendations are as follows:

Weight	Posology
15–30 kg	Combination with two antibiotics: Dafrazol 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together two times daily for one week.
31–40 kg	Combination with two antibiotics: Dafrazol 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered two times daily for one week.
> 40 kg	Combination with two antibiotics: Dafrazol 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered two times daily for one week.

#### **4.2.4. Method of administration**

It is recommended to take Dafrazol capsules in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

For patients with swallowing difficulties and for children, the capsule can be opened and the content can be taken with half a glass of water or after mixing the contents in a slightly acidic fluid e.g. fruit juice or applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water.

Alternatively, patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

### 4.3 Contraindications

- Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1.
- Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

### 4.4 Special warning and precautions for use

#### 4.4.1 General information

- In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
- Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.
- Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
- Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered.
- An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
- Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. Severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
- For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals

should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

- Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors.
- Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
- Subacute cutaneous lupus erythematosus (SCLE). Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Dafrazol. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.
- Interference with laboratory tests. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.
- Dafrazol contain sucrose (about 50 mg per capsule). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

#### 4.4.2 Pediatric population

No additional information

#### 4.5 Interactions with other medicinal products and other forms of interactions

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

##### **Active substances with pH dependent absorption**

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

- **Nelfinavir, atazanavir**

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

Concomitant administration of omeprazole with nelfinavir is contraindicated. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition. Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

- **Digoxin**

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

- **Clopidogrel**

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

- **Other active substances**

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

#### **Active substances metabolised by CYP2C19**

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also

metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

- **Cilostazol**

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

- **Phenytoin**

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

#### **Unknown mechanism**

- **Saquinavir**

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

- **Tacrolimus**

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

- **Methotrexate**

When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

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

- **Inhibitors of CYP2C19 and/or CYP3A4**

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose

adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

- **Inducers of CYP2C19 and/or CYP3A4**

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

## **4.6 Fertility, pregnancy and lactation**

### **4.6.1 Fertility**

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

### **4.6.2 Pregnancy**

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

### **4.6.3 Lactation**

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

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

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

## **4.8 Undesirable effects**

The frequencies of adverse reactions reported with omeprazole are defined as:

- very common ( $\geq 1/10$ )
- common ( $\geq 1/100$  to  $< 1/10$ )
- uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- very rare ( $< 1/10,000$ )
- not known (cannot be estimated from the available data)

*Summary of the safety profile*

<b>System of Organ Class</b>	<b>Adverse reaction</b>
<b>Frequency</b>	
<b>Blood and lymphatic system disorders</b>	
Rare	Leukopenia, thrombocytopenia
Very rare	Agranulocytosis, pancytopenia
<b>Immune system disorders</b>	
Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
<b>Metabolism and nutrition disorders</b>	
Rare	Hyponatraemia
Not known	Hypomagnesaemia
<b>Psychiatric disorders</b>	
Uncommon	Insomnia
Rare	Agitation, confusion, depression
Very rare	Aggression, hallucinations
<b>Nervous system disorders</b>	
Common	Headache
Uncommon	Dizziness, paraesthesia, somnolence
Rare	Taste disturbance
<b>Eye disorders</b>	
Rare	Blurred vision
<b>Ear and labyrinth disorders</b>	
Uncommon	Vertigo
<b>Respiratory, thoracic and mediastinal disorders</b>	
Rare	Bronchospasm
<b>Gastrointestinal disorders</b>	

<b>System of Organ Class</b>	<b>Adverse reaction</b>
<b>Frequency</b>	
Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare	Dry mouth, stomatitis, gastrointestinal candidiasis
Not known	Microscopic colitis
<b>Hepatobiliary disorders</b>	
Uncommon	Increased liver enzymes
Rare	Hepatitis with or without jaundice
Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Dermatitis, pruritus, rash, urticaria
Rare	Alopecia, photosensitivity
Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known	Subacute cutaneous lupus erythematosus
<b>Musculoskeletal and connective tissue disorders</b>	
Uncommon	Fracture of the hip, wrist or spine
Rare	Arthralgia, myalgia
Very rare	Muscular weakness
<b>Renal and urinary disorders</b>	
Rare	Interstitial nephritis
<b>Reproductive system and breast disorders</b>	
Very rare	Gynaecomastia
<b>General disorders and administration site conditions</b>	
Uncommon	Malaise, peripheral oedema

System of Organ Class Frequency	Adverse reaction
Rare	Increased sweating

### Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long-term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

### 4.9 Overdose

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

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

## 5- PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

#### Mechanism of action

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

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

### **Pharmacodynamic effects**

#### **Effect on gastric acid secretion**

Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour gastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing. Oral dosing with omeprazole 20 mg maintains an gastric pH of  $\geq 3$  for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and gastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

#### **Effect on *Helicobacter pylori***

*H. pylori* is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with, high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

#### **Other effects related to acid inhibition**

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

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

*Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

### **Paediatric population**

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 gastro-oesophageal reflux disease 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 *H. pylori* in children

A randomised, double blind clinical study (Heliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis: *H. 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 any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

## **5.2 Pharmacokinetic properties**

### **Absorption**

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

### **Distribution**

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

### **Biotransformation**

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

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

### **Elimination**

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

### **Linearity/non-linearity**

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone). No metabolite has been found to have any effect on gastric acid secretion.

### **Special populations**

#### **Hepatic impairment**

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

**Renal impairment**

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

**Elderly**

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

**Paediatric population**

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**

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H<sub>2</sub>-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

**6- PHARMACEUTICAL PARTICULARS****6.1 List of excipients**Content of the capsule

- Sugar spheres (sucrose and maize starch)
- Sodium starch glycolate
- Sodium laurilsulfate
- Povidone
- Hypromellose phthalate
- Sucrose
- Hypromellose
- Mannitol
- Diacetylated monoglycerides
- Talc

Capsule shell

- Gelatin
- Titanium dioxide E171

- Red iron oxide E172
- Quinoline yellow E104
- Indigocarmine E132.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

Store below 30° C, in the original packaging, protected from light and moisture.

## 6.5 Nature and contents of container

Hard gelatin, size 2 capsule with yellow opaque body and dark green cap, containing white to whitish spherical, odourless and tasteless, gastro-resistant micro pellets.

The capsules are packaged in aluminum/aluminum blisters.

Cardboard box with 14 capsules (2 blisters of 7).

Cardboard box with 28 capsules (4 blister of 7).

## 6.6 Special precautions for disposal and other handlings

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7- MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

### 7.1 Marketing Authorisation Holder;

Dafra Pharma GmbH, Mühlenberg 7, 4052 Bâle, Switzerland

### 7.2 Manufacturer

Nobel İlaç Sanayii ve Ticaret A.Ş., Sancaklar 81100 Düzce, Turkey.

## 8- MARKETING AUHORISATION NUMBER

See list of MAs per country

## 9- DATE OF FIRST REGISTRATION

See list of MAs per country

**10- DATE OF REVISION OF TEXT**

November 2021 ( section 6.4)