| | |
|---|---|
| Product Trade Name | **DAFRAZOL® IV**<br>*Name of product in manufacturing country = ESELAN 40 mg / vial* |
| Drug Product name, strength and pharmaceutical form | Omeprazole 40 mg, Powder and solvent for solution for injection |
| Dossier ID | CPR-RAD-**SDZOLIV4-RW** |
| **Module 1.6.1** | **Product information – Prescribing information (SmPC)** |

# MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

## 1.6 Product Information

### 1.6.1 Prescribing information (SmPC)

Enclosed is the section 1.5.1 Summary of Product Characteristics (SmPC) from the dossier CPR-RAD-SDZOLIV4-v1.0.

# Summary of Product Characteristics

## 1-NAME OF THE MEDICINAL PRODUCT (FPP)

**DAFRAZOL® IV**

*Omeprazole*

### 1.1 Strength

40 mg ( 4 mg/ml following reconstitution with the enclosed solvent)

### 1.2 Pharmaceutical form

Powder and solvent for solution for injection

## 2- QUALITATIVE AND QUANTITATIVE COMPOSITION

### 2.1 Qualitative declaration

Omeprazole sodium

For the full list of excipients, see section 6.1

### 2.2 Quantitative declaration

Each vial of powder for solution for injection contains 42.6 mg of omeprazole sodium, corresponding to 40 mg of omeprazole.

After reconstitution with the solvent, 1 ml contains 4.26 mg of omeprazole sodium, corresponding to 4 mg of omeprazole.

## 3- PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to almost white cake

Solvent: colourless solution

Solution following reconstitution of powder vial with the solvent ampoule: clear, colourless to pale yellow solution

## 4- CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dafrazol IV for intravenous use is indicated in adults as an alternative to oral treatment for:

**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

### 4.2 Posology and mode of administration

#### 4.2.1 Posology

**Adults :** alternative to oral therapy.

- In patients for whom the oral route is not appropriate, 40 mg of Dafrazol IV is recommended once daily.
- In patients with Zollinger-Ellison syndrome, the recommended initial dose of intravenous Dafrazol IV is 60 mg daily.
- Higher daily doses may be necessary and an individual dose adjustment should be made. When the required dose exceeds 60 mg daily, the dose should be divided into two daily doses.

**4.2.2 Special populations**

***Impaired renal function***

No dosage adjustment is necessary in case of renal insufficiency.

***Impaired hepatic function***

A daily dose of 10 mg-20 mg may be sufficient in patients with hepatic impairment.

***Elderly***

No dose adjustment is necessary in the elderly.

**4.2.3 Paediatric population**

Experience with the use of intravenous omeprazole is limited in children.

**4.2.4. Method of administration**

- Dafrazol IV powder is reconstituted with the Dafrazol IV solvent to a solution for intravenous injection .
- After reconstitution, the injection should be administered slowly over at least 2 minutes with a maximum flow rate of 4 ml per minute.
- For instructions on reconstitution of the product before administration , see section 6.6.

**4.3 Contraindications**

- Hypersensitivity to the active substance, to 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 (omeprazole) treatment. 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.

### 4.4.2 Paediatric population

Experience with the use of intravenous omeprazole is limited in children

## 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 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 Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

- **Phenytoin**

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

Unknown mechanism

- **Saquinavir**

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

- **Tacrolimus**

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

- **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 Pregnancy, lactation and fertility

### 4.6.1 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.

### 4.6.2 Lactation

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

**4.6.3 Fertility**

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

**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**

Summary of the safety profile

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

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

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

| **System of Organ Class**<br>**Frequency** | **Adverse reaction** |
|---|---|
| **Blood and lymphatic system disorders** | |
| Rare | Leukopenia, thrombocytopenia |
| Very rare | Agranulocytosis, pancytopenia |
| **Immune system disorders** | |
| Rare | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock |
| **Metabolism and nutrition disorders** | |
| Rare | Hyponatraemia |
| Not known | Hypomagnesaemia |
| **Psychiatric disorders** | |

| System of Organ Class<br>Frequency | Adverse reaction |
|---|---|
| Uncommon | Insomnia |
| Rare | Agitation, confusion, depression |
| Very rare | Aggression, hallucinations |
| **Nervous system disorders** | |
| Common | Headache |
| Uncommon | Dizziness, paraesthesia, somnolence |
| Rare | Taste disturbance |
| **Eye disorders** | |
| Rare | Blurred vision |
| **Ear and labyrinth disorders** | |
| Uncommon | Vertigo |
| **Respiratory, thoracic and mediastinal disorders** | |
| Rare | Bronchospasm |
| **Gastrointestinal disorders** | |
| Common | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign) |
| Rare | Dry mouth, stomatitis, gastrointestinal candidiasis |
| Not known | Microscopic colitis |
| **Hepatobiliary disorders** | |
| Uncommon | Increased liver enzymes |
| Rare | Hepatitis with or without jaundice |
| Very rare | Hepatic failure, encephalopathy in patients with pre-existing liver disease |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon | Dermatitis, pruritus, rash, urticaria |
| Rare | Alopecia, photosensitivity |
| Very rare | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) |
| Not known | Subacute cutaneous lupus erythematosus |
| **Musculoskeletal and connective tissue disorders** | |
| Uncommon | Fracture of the hip, wrist or spine |
| Rare | Arthralgia, myalgia |
| Very rare | Muscular weakness |
| **Renal and urinary disorders** | |
| Rare | Interstitial nephritis |
| **Reproductive system and breast disorders** | |

| System of Organ Class<br>Frequency | Adverse reaction |
|---|---|
| Very rare | Gynaecomastia |
| **General disorders and administration site conditions** | |
| Uncommon | Malaise, peripheral oedema |
| Rare | Increased sweating |

Cases of irreversible visual impairment have been reported in an isolated number of patients with severe systemic impairment who received intravenous omeprazole, mainly at high doses, but without confirmation of a causal link.

**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.

In clinical studies, intravenous doses of up to 270 mg on a single day and up to 650 mg over a three-day period did not result in dose-related adverse events.

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 $H^+$ $K^+$-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***

Intravenous omeprazole produces a dose dependent inhibition of gastric acid secretion in humans. In order to immediately achieve a similar reduction of intragastric acidity as after repeated dosing with 20 mg orally, a first dose of 40 mg intravenously is recommended. This results in an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90% for both IV injection and IV infusion.

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.

***<u>Other effects related to acid inhibition</u>***

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.

## 5.2 Pharmacokinetic properties

**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).

## 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 $H_2$-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

Vial with powder of active substance

- Sodium hydroxide (to adjust the pH).

Solvent ampoule

- Citric acid monohydrate,
- Macrogol 400,
- Water for injection.

### 6.2 Incompatibilities

Dafrazol IV should not be mixed with products other than those mentioned in section 6.6.

### 6.3 Shelf life

3 years (36 months)

### 6.4 Special precautions for storage

Store below 30 ° C.

Keep the containers (vial and ampoule) in the original package in order to protect from light.

Reconstituted solution: The chemical and physical in-use stability has been demonstrated for 4 hours at room temperature (25 ° C) and for 12 hours refrigerated ( 2°C-8°C).

From a microbiological point of view, the product should be used immediately unless the solution is reconstituted under controlled and validated aseptic conditions.

**6.5 Nature and contents of container**

Powder vial: Transparent type I glass vial of 12 ml containing a white or almost white cake (lyophilisated powder) , closed with a bromobutyl stopper and aluminium flip-off cap.

Solvent ampoule: Type I transparent glass ampoule with 10 ml of clear, colourless solution.

Cardboard box with plastic tray carrying the vial , the ampoule and a patient leaflet.

**6.6 Special precautions for disposal and other handlings**

The solution for injection of Dafrazol IV is obtained by dissolving the powder with the accompanying solvent. No other solvent should be used.

The stability of omeprazole is influenced by the pH of the solution for injection, which is why no other solvent or quantity should be used for dilution before injection of the solution.

Use only clear, colourless or very slightly yellow brown solutions. Do not use when the solution presents a brown colour.

**Preparation**

**Note: Steps 1 to 5 should be performed immediately one after the other**

1. With a syringe take all the solvent from the ampoule (10 ml).
2. Add 5 ml of this solvent to the ampoule containing the lyophilisate of omeprazole.
3. Remove air from the ampoule as much as possible with the syringe to facilitate the addition of the remaining solvent.
4. Add the remaining solvent into the ampoule making sure the syringe is empty.
5. Stir and shake the ampoule to ensure that the lyophilisate of omeprazole is dissolved.

After reconstitution, the injection should be administered slowly over at least 2 minutes with a maximum flow rate of 4 ml per minute.

No special requirements for disposal.

- **Note**

  For use in infusion fluids (sodium chloride 9 mg/ml (0.9%) or glucose solution 50 mg/ml (5%) , the preparation , use, duration and storage conditions during use are the responsibility of the health care professional/user.

**7- MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS**

**7.1 Marketing Authorisation Holder;**

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

**7.2 Manufacturer**

Anfarm Hellas S.A., 61st km. Nat. Rd. Athens, Lamia, Schimatari Viotias, 32009, Greece.

**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**

January 2020