

# **Public Assessment Report**

**Omeprazole 40mg Powder for Solution for Infusion**

**(omeprazole sodium)**

**PL 10622/0232**

# **OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION**

## **(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

**UKPAR**

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# **OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION**

## **(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Pliva Pharma Limited a Marketing Authorisation (licence) for the medicinal product Omeprazole 40mg Powder for Solution for Infusion (PL 10622/0232). This is a prescription only medicine [POM] used to prevent acid aspiration (where the stomach acid is breathed into the lungs). It is also used, in the short term, to treat stomach ulcers, intestinal ulcers and related conditions.

The active substance omeprazole belongs to a group of medicines known as proton pump inhibitors, which help to reduce and control stomach acid production.

The clinical data presented to the MHRA, before licensing, demonstrated that Omeprazole 40mg Powder for Solution for Infusion is essentially similar or equivalent to the approved product, Losec Infusion 40mg, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Omeprazole 40mg Powder for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

# **OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION**

## **(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

### **SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted a Marketing Authorisation for the medicinal product Omeprazole 40mg Powder for Solution for Infusion (PL 10622/0232) to Pliva Pharma Limited on 11 October 2006. Omeprazole 40mg Powder for Solution for Infusion is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Losec powder for solution for infusion 40mg, which was first authorised in Denmark in March 1990.

This product contains the active ingredient omeprazole and is indicated for the prophylaxis of acid aspiration and, in patients who are unable to take oral therapy, for the short term treatment (up to 5 days) of reflux oesophagitis, duodenal and benign gastric ulcers, including those complicating NSAID therapy e.g. peri-operative use.

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. 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.

## **PHARMACEUTICAL ASSESSMENT**

<b>LICENCE No.:</b>	<b>PL 10622/0232</b>
<b>PROPRIETARY NAME:</b>	<b>Omeprazole 40mg Powder for Solution for Infusion</b>
<b>ACTIVE:</b>	<b>Omeprazole (omeprazole sodium formed <i>in situ</i>)</b>
<b>COMPANY NAME:</b>	<b>Pliva Pharma Ltd.</b>
<b>EC ARTICLE:</b>	<b>10.1(a)iii of Directive 2001/83/EC</b>
<b>LEGAL STATUS:</b>	<b>POM</b>

### **INTRODUCTION**

This national abridged application is for a powder for solution for infusion containing 40 mg of the proton pump inhibitor omeprazole. The applicant has proposed that the product is indicated for the prophylaxis of acid aspiration and for patients unable to take oral therapy for the short term treatment (up to 5 days) of reflux oesophagitis, duodenal and benign gastric ulcers, including those complicating NSAID therapy eg, peri-operative use.

This application has been made under the first paragraph of Article 10.1(a)(iii) of Directive 2001/83/EC claiming essential similarity to the original product, Losec powder for solution for infusion 40mg authorised to AstraZeneca in Denmark in March 1990. The reference medicinal product in the UK is Losec Infusion 40mg (PL 17901/0136) authorised to AstraZeneca UK Limited in May 2002 following a change of ownership from Astra Pharmaceuticals Limited (PL 00017/0400) authorised in November 1998.

There is no paediatric development plan for this product.

The proposed product has not been authorised to the applicant or to a related company in any other European Union (EU) Member State, nor is it the subject of any pending application in any other EU Member State.

### **COMMON TECHNICAL DOCUMENT SUMMARIES**

#### **Introduction**

A satisfactory introduction has been provided.

#### **Quality Overall Summary (QOS)**

A satisfactory Quality Overall Summary has been provided.

### **ACTIVE SUBSTANCE**

#### **General information**

#### ***Nomenclature***

rINN: omeprazole

(RS)-5-methoxy-2-[[[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-1H-benzimidazole

## ***Structure***



MW: 345.4

## ***General properties***

White or almost white powder, very slightly soluble in water, soluble in methylene chloride, sparingly soluble in alcohol and methanol. It dissolves in dilute solutions of alkali hydroxides. Data has been provided to show that the crystalline form is consistent with the Ph.Eur. standard.

## **Manufacture**

### ***Manufacturer***

A suitable manufacturing site has been named.

### ***Manufacturing process description and process controls***

A copy of the current Certificate of Suitability has been provided for the proposed source of active substance.

### ***Control of materials***

Supported by Certificate of Suitability.

TSE status: A declaration has been provided confirming that none of the materials used in the manufacturing process are of animal origin.

### ***Controls of critical steps and intermediates***

Supported by Certificate of Suitability.

### ***Process validation and/or evaluation***

Supported by Certificate of Suitability.

## **Characterisation**

### ***Elucidation of structure and other characteristics***

Supported by Certificate of Suitability.

### ***Impurities***

Supported by Certificate of Suitability.

## **Control of active substance**

### ***Specification***

Omeprazole complies with the requirements of the Ph.Eur. monograph for omeprazole.

The active substance manufacturer also applies additional specifications.

### ***Analytical procedures***

#### ***Validation of analytical procedures***

The analytical methods used are those described in the Ph.Eur. monograph, supplemented by in-house methods.

### ***Batch analyses***

Certificates of Analysis have been provided for batches manufactured at the proposed site. The batches comply with the proposed active substance specification.

### ***Justification of specification***

The applicant has confirmed that the specification is in accordance with the Certificate of Suitability.

## **Reference standards or materials**

Satisfactory Certificates of Analysis have been provided for the primary, secondary and impurity reference standards.

## **Container closure system**

Satisfactory details have been provided. Acceptable specifications, Certificates of Analysis and food contact declaration have been provided.

## **Stability**

### ***Stability summary and conclusions***

Stability data have been provided for batches of active substance manufactured at the proposed site. The batches were stored in containers manufactured from the materials as proposed for the commercial packs, to simulate the bulk containers.

Analytical methods applied were those used for routine batch release.

Stability data provided: 25°C/60%, 2-8°C.

The active substance manufacturer has proposed an acceptable re-test period based on the available data



### ***Post-approval stability protocol and stability commitment***

A satisfactory commitment was provided.

## **MEDICINAL PRODUCT**

### **Description and composition of the medicinal product**

#### Composition and function of ingredients

<b>Ingredient</b>	<b>Quantity</b>	<b>Reference Standard</b>
Omeprazole	40.000 mg	Ph.Eur.
Sodium hydroxide 1N		Ph.Eur.
Disodium edetate		Ph.Eur.

No Genetically Modified Organisms are included in the product.

### **Pharmaceutical development**

#### ***Components of the medicinal product***

The function of each ingredient included in the product has been described.

#### ***Formulation development***

A summary of the development studies has been provided particularly with respect to optimising the formulation and lyophilisation cycle. This is satisfactory.

### **Manufacture**

#### ***Manufacturer(s)***

The product will be released at Sofarimex Industria Quimica e Farmaceutica Lda, Agualva-2735-213, Cacém, Portugal.

Satisfactory details of inspection and compliance with Good Manufacturing Practice have been provided.

#### ***Batch formula***

A satisfactory formula has been provided for the manufacture of a suitable batch size.

#### ***Description of manufacturing process and process controls***

Satisfactory description provided.

### ***Control of critical steps and intermediates***

Satisfactory tests and acceptance criteria have been set for in-process testing.

### ***Process validation and/or evaluation***

The manufacturing process has been satisfactorily validated.

### **Control of excipients**

#### ***Specifications***

All ingredients comply with relevant Ph.Eur. monographs.

Satisfactory supplier and finished product manufacturer Certificates of Analysis have been provided for each ingredient.

#### ***Excipients of human or animal origin***

The marketing authorisation application (MAA) form indicates that no materials of animal or human origin are contained in or used in the manufacturing process for the proposed product. Satisfactory declarations have been provided from the suppliers.

### **Control of medicinal product**

#### ***Specification***

The proposed finished product specification is acceptable.

#### ***Analytical procedures***

##### ***Validation of analytical procedures***

Satisfactory validation details provided.

#### ***Batch analyses***

Batch analysis data have been provided. The batches were manufactured at the proposed commercial site and packed in the proposed commercial packs. All batches comply with the proposed specification.

#### ***Characterisation of impurities***

Satisfactory.

#### ***Justification of specifications***

A justification for the release and shelf life limits has been provided.

## **Reference standards or materials**

Satisfactory Certificates of Analysis have been provided for the working standard and for impurities. In addition, documentation has been provided for the primary reference standard. The batch of primary reference standard has been used to characterise the in-house working standard.

## **Container-closure system**

The product is presented in clear colourless 15ml Type I glass vials with chlorobutyl stoppers and an aluminium flip-off cap.

The vials and stoppers meet the requirements of the relevant Ph.Eur. monographs. The stoppers comply with Directive 94/62/EC with respect to absence of added lead, cadmium, hexavalent chromium and mercury.

Satisfactory specifications and Certificates of Analysis/conformity have been provided for representative batches of the packaging components.

## **Stability**

### ***Stability summary and conclusion***

Stability data were provided for 3 pilot batches. The batches were manufactured at the proposed commercial site and packed in the proposed commercial packs.

The analytical methods used are the same as for routine batch release.

Stability data provided: 25°C/60%, 30°C/65%, 30°C/70% and 40°C/75%, stored inverted and upright

The stability data support a shelf-life of 2 years for product carrying the storage recommendations “Do not store above 25°C. Keep the vial in the outer carton”. The proposed in-use shelf life of 6 hours is supported when reconstituted in 5% glucose.

### ***Post-approval stability protocol and stability commitment***

A commitment has been provided that industrial size batches will be placed on store and tested in accordance with ICH.

## **BIOEQUIVALENCE/BIOAVAILABILITY**

No bioequivalence study is required to support this application.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)  
LABELLING  
PATIENT INFORMATION LEAFLET**

Satisfactory.

**CONCLUSIONS**

A marketing authorisation may be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required.

## **CLINICAL ASSESSMENT**

<b>LICENCE No.:</b>	<b>PL 10622/0232</b>
<b>PROPRIETARY NAME:</b>	<b>Omeprazole 40mg Powder for Solution for Infusion</b>
<b>ACTIVE:</b>	<b>Omeprazole (omeprazole sodium formed <i>in situ</i>)</b>
<b>COMPANY NAME:</b>	<b>Pliva Pharma Ltd.</b>
<b>EC ARTICLE:</b>	<b>10.1(a)iii of Directive 2001/83/EC</b>
<b>LEGAL STATUS:</b>	<b>POM</b>

### **INTRODUCTION**

This is a national abridged application for Omeprazole 40mg to be used intravenously, under Article 10.1(a)(iii), first paragraph, cross-referring to Losec Infusion 40mg marketed by AstraZeneca UK Ltd, PL 17901/0136, the original product being first authorised in Denmark on 20 March 1990.

### **BACKGROUND**

The indications are specific for this method of delivery, the drug being well established for use in these indications.

### **INDICATIONS**

The indications are consistent with the licensed indications approved for the UK reference product and are, therefore, satisfactory.

### **DOSE & DOSE SCHEDULE**

See Summary of Product Characteristics. The proposed posology is in line with currently agreed requirements and is therefore satisfactory. The powder is for intravenous administration only and must not be given by any other route. It should be dissolved in 5% dextrose and should then be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions.

### **TOXICOLOGY**

No formal data are presented under this heading and none are required for this application.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacodynamics**

Omeprazole is commonly described as being a “proton pump inhibitor”. It acts directly and dose dependently through the inhibition of the H<sup>+</sup> K<sup>+</sup>-ATPase enzyme which is responsible for the secretion of gastric acid from the parietal cells (border cells) of the stomach. By acting intra-cellularly it reduces both basal and stimulated acid secretion, irrespective of the type of stimulus.

## **Pharmacokinetics**

See Summary of Product Characteristics.

## **EFFICACY**

No new data are submitted and none are required for this application. The efficacy of omeprazole has been well documented.

## **SAFETY**

No new data are submitted and none are required for this application.

## **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

## **PATIENT INFORMATION LEAFLET (PIL)**

## **LABELLING**

Satisfactory.

## **DISCUSSION**

The clinical data submitted by the applicant are sufficient to establish efficacy and safety in the requested indications. No bioequivalence study is required. The SPC and PIL are satisfactory.

## **CONCLUSION**

Marketing authorisation may be granted.

## **OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Omeprazole 40mg Powder for Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

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

### **EFFICACY**

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Losec Infusion 40mg (PL 17901/0136). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those of Losec Infusion 40mg.

### **RISK-BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.



# OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION

## (OMEPRAZOLE SODIUM)

PL 10622/0232

### STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Omeprazole 40mg Powder for Solution for Infusion on 30 April 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 9 November 2004.
3	Further information (clinical) was requested from the company on 12 November 2004.
4	The MHRA's assessment of the submitted quality data was completed on 10 March 2005.
5	Further information (quality) was requested from the company on 10 March 2005.
6	The applicant's responses to further information requests (quality and clinical) were received 4 July 2005.
7	Further information (quality) was requested from the company on 23 January 2006.
8	The applicant's response to further information request (quality) was sent in a letter dated 20 March 2006.
9	The applicant requested certain changes to the quality data on 4 July 2006.
10	The application was determined on 10 October 2006.

**OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION  
(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Omeprazole 40mg Powder for Solution for Infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for solution for infusion contains Omeprazole Sodium, equivalent to Omeprazole 40mg.

### 3. PHARMACEUTICAL FORM

Powder for solution for infusion.  
White to almost white lyophilised powder.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Prophylaxis of acid aspiration.  
In patients who are unable to take oral therapy for the short term treatment (up to 5 days) of reflux oesophagitis, duodenal and benign gastric ulcers, including those complicating NSAID therapy e.g. peri-operative use.

#### 4.2 Posology and method of administration

##### Dosage

##### Adults only

**Prophylaxis of acid aspiration** Omeprazole 40mg Infusion to be given as an intravenous infusion, to be completed one hour before surgery.

**Treatment in patients where oral therapy is inappropriate e.g. in severely ill patients with either reflux oesophagitis, duodenal ulcer or gastric ulcer:**

Omeprazole 40mg Infusion given as an intravenous infusion once daily is recommended for up to 5 days.

The i.v. infusion produces an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90%.

Clinical experience in Zollinger Ellison syndrome is limited (see section 5.1 Pharmacodynamic properties).

##### Administration

Omeprazole 40mg Powder for Solution for Infusion is for intravenous administration ONLY and must NOT be given by any other route.

Omeprazole 40mg Powder for Solution for Infusion should only be dissolved in 100ml 5% glucose for infusion. No other solutions for i.v. infusion should be used.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/ dilution (etc) has taken place in controlled and validated aseptic conditions.

The duration of administration of the infusion should be 20-30 minutes.

Use in the Elderly:

Dosage adjustment is not necessary.

Use in Children:

There is limited experience of use in children.

Impaired renal function:

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

Impaired hepatic function:

As half-life is increased in patients with impaired hepatic function, the dose requires adjustment and a daily dose of 10mg - 20mg may be sufficient.

#### **4.3 Contraindications**

Known hypersensitivity to omeprazole or to any of the other constituents of the formulation.

#### **4.4 Special warnings and precautions for use**

When gastric ulcer is suspected the possibility of malignancy should be excluded before treatment with Omeprazole 40mg Infusion is instituted, as treatment may alleviate symptoms and delay diagnosis.

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 medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during omeprazole therapy 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 and warfarin. Monitoring of patients receiving phenytoin or warfarin is recommended and a reduction of phenytoin or warfarin dose may be necessary when omeprazole is added to treatment. However, concomitant treatment with omeprazole 20mg orally daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. Similarly, concomitant treatment with omeprazole 20mg orally daily did not change coagulation time in patients on continuous treatment with warfarin.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant oral administration. There is no interaction with metronidazole or amoxicillin. These antimicrobials are used together with omeprazole for eradication of *Helicobacter pylori*.

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, ciclosporin, lidocaine, quinidine, estradiol, or antacids when omeprazole is given orally. The absorption of omeprazole given orally 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 led to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

Interaction with other drugs also metabolised via the cytochrome P450 system cannot be excluded.

#### **4.6 Pregnancy and lactation**

##### **Use in pregnancy**

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

##### **Use in lactation**

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

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

No effects are foreseen.

#### **4.8 Undesirable effects**

Omeprazole is 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
Uncommon	≥1/1000 and < 1/100
Rare	< 1/1000

<b>Common</b>	<i>Central and peripheral nervous system:</i> <i>Gastrointestinal:</i>	Headache Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
<b>Uncommon</b>	<i>Central and peripheral nervous system:</i>  <i>Hepatic:</i> <i>Skin:</i>	Dizziness, paraesthesia, light headedness, feeling faint, somnolence, insomnia and vertigo. Increased liver enzymes. Rash and/or pruritus. Urticaria. Malaise.
<b>Rare</b>	<i>Other:</i> <i>Central and peripheral nervous system:</i>  <i>Endocrine:</i> <i>Gastrointestinal:</i>  <i>Haematological:</i>  <i>Hepatic</i>   <i>Musculoskeletal</i>  <i>Reproductive system and breast disorders</i> <i>Skin</i>	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients. Gynaecomastia. Dry mouth, stomatitis and gastrointestinal candidiasis. Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia. Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure.  Arthritic and myalgic symptoms and muscular weakness.  Impotence Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic

*Other*

epidermal necrolysis (TEN), alopecia. Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia

Isolated cases of irreversible visual impairment have been reported in critically ill patients who have received omeprazole infusion, particularly at high doses, however no causal relationship has been established.

#### **4.9 Overdose**

Intravenous doses of up to 270mg on a single day and up to 650mg over a three-day period have been given in clinical trials without any dose related adverse effects.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic Properties**

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 control of gastric acid secretion with once daily dosing.

Intravenous administration of omeprazole results in an immediate reduction of intragastric acidity and a mean decrease over 24 hours of approximately 90% in patients with duodenal ulcer disease. A single 40mg i.v. dose has similar effect on intragastric acidity over a 24 hour period as repeated oral dosing with 20mg once daily. A higher dose of 60mg i.v. twice daily has been used in a clinical study in patients with Zollinger-Ellison syndrome.

#### 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<sup>+</sup>, K<sup>+</sup>, -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. No tachyphylaxis has been observed during treatment with omeprazole.

## 5.2. Pharmacokinetic Properties

### *Distribution*

The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiency. In the elderly and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. The plasma protein binding of omeprazole is about 95%.

### *Metabolism and excretion*

The average half-life of the terminal phase of the plasma concentration-time curve following i.v. administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during treatment.

Omeprazole is completely metabolised by the cytochrome P450 system, mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an intravenously given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

Elimination of omeprazole is unchanged in patients with reduced renal function. The elimination half-life is increased in patients with impaired liver function, but omeprazole has not shown any accumulation with once daily oral dosing.

## 5.3. Preclinical Safety Data

*Animal Toxicology:* 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

Sodium hydroxide  
Disodium edetate



## **6.2 Incompatibilities**

No other drugs should be mixed with reconstituted Omeprazole 40mg Powder for Solution for Infusion.

## **6.3 Shelf life**

Unopened pack: 2 years.

Reconstituted solution: 6 hours

Chemical and physical in use stability of the product has been shown for 6 hours once dissolved in 5% glucose and stored at 25°C. From a microbiological point of view, once reconstituted the infusion should be initiated immediately.

## **6.4 Special precautions for storage**

Do not store above 25°C. Keep the vial in the outer carton.

## **6.5 Nature and contents of container**

Pack of 1 or 5, clear, Type I, glass 15ml vials containing 40mg omeprazole with a chlorobutyl stopper and aluminium flip-off cap.

## **6.6 Instructions for use/handling**

Omeprazole 40 mg powder for solution for infusion should be administered as intravenous infusion (over a period of 20 to 30 minutes or more).

Omeprazole 40 mg powder for solution for infusion should only be reconstituted by dissolving the freeze-dried powder in 100 ml of 5% glucose. No other solutions for infusion should be used.

Use on one patient during one treatment only.

DO NOT USE unless the infusion is fully reconstituted in 100ml 5% glucose or if there are any particles present in the reconstituted solution.

To prepare the infusion:

1. Reconstitute the vial with a volume of 5% glucose solution that is sufficient to dissolve the freeze-dried powder.
2. Transfer this reconstituted solution to the infusion bottle or bag.
3. Repeat the steps above as many times as necessary to ensure that all the freeze-dried powder is completely dissolved in the 100 ml of 5% glucose.

For infusions in flexible containers an alternative method with a double ended transfer needle may be used:

1. Attach one end of the needle to the injection membrane of the infusion bag and the other end to the vial containing the freeze-dried omeprazole.
2. Pump the infusion back and forward between the bag and the vial to dissolve the omeprazole.
3. Continue pumping until all the powder is dissolved. Withdraw the empty vial and the needle from the bag.

**7.       MARKETING AUTHORISATION HOLDER**

PLIVA Pharma Ltd.  
Vision House  
Bedford Road  
Petersfield  
Hampshire, GU32 3QB

**8.       MARKETING AUTHORISATION NUMBER**

PL 10622/0232

**9        DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

11/10/2006

**10       DATE OF REVISION OF THE TEXT**

11/10/2006

Patient Information Leaflet

**OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION**

**(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

## PATIENT INFORMATION LEAFLET

### Omeprazole 40mg Powder for Solution for Infusion

Read this entire leaflet carefully before the doctor or nurse starts to give you this medicine. If this medicine is for a child and you are their parent or guardian, you should read the information on their behalf before this medicine is given.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or nurse.

This leaflet contains information on:

1. What is Omeprazole 40mg Powder for Solution for Infusion and what is it used for?
2. Before you are given Omeprazole 40mg Powder for Solution for Infusion.
3. How Omeprazole 40mg Powder for Solution for Infusion is given.
4. Possible side effects.
5. Storing Omeprazole 40mg Powder for Solution for Infusion.

The name of your medicine is Omeprazole 40mg Powder for Solution for Infusion.

The active substance is omeprazole (as omeprazole sodium).

The powder will be mixed with a liquid, to make a solution which will be given as an infusion (a 'drip').

Other ingredients include disodium edetate and sodium hydroxide.

#### Marketing Authorisation Holder:

PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB.

#### Manufacturer:

SOFARIMEX Industria Química e Farmaceutica Lda, Av. Indústrias, Alto do Colaride, Agualva-2735-213, Cacém, Portugal.

#### 1. What is Omeprazole 40mg Powder for Solution for Infusion and what is it used for?

Omeprazole 40mg Powder for Solution for Infusion comes in a single vial pack or packs of five vials, each containing 40mg omeprazole. This powder is ready to be reconstituted (dissolved in liquid), to be given by infusion (see under 'How Omeprazole 40mg Powder for Solution for Infusion is given').

Omeprazole is a type of gastric proton pump inhibitor, which reduces and controls stomach acid production. Omeprazole is used to treat

duodenal ulcers (in the upper part of the intestine), some gastric ulcers (in the stomach), reflux oesophagitis and oesophageal reflux disease (where the backwash of stomach acid causes heartburn and other indigestion symptoms) and the prevention of acid aspiration (where the stomach acid is breathed into the lungs and causes damage – this usually occurs during an operation). Omeprazole Infusion is used for the short term treatment when swallowing is difficult.

#### 2. Before you are given Omeprazole 40mg Powder for Solution for Infusion.

Please ask yourself the following question:

- Have you ever taken a medicine containing omeprazole, any other gastric proton pump inhibitor, or any of the other ingredients listed above and had an unusual or allergic reaction?

If the answer is YES, tell the doctor or nurse who will be giving you this medicine, as soon as possible and **before** the injection or infusion is given to you. Your doctor will then decide whether you should receive omeprazole.

If you have an ulcer your doctor may wish to do some tests to check omeprazole is a suitable type of treatment.

This medicinal product contains less than 1 mmol (23mg) sodium per 40mg dose, i.e. essentially 'sodium free'.

You should ask your doctor or nurse for a patient information leaflet about the 5% glucose solution that the powder for infusion has been dissolved in.

Treatment with drugs which reduce stomach acid, such as omeprazole, can increase the risk of stomach infection.

#### Taking other medicines

Omeprazole may interact with other medicines that you may be taking.

The levels of ketoconazole and itraconazole may decrease if these are taken with omeprazole.

The levels of diazepam, warfarin and phenytoin may be affected if these are taken with omeprazole, and doses of warfarin and phenytoin may have to be altered.

The levels of both clarithromycin and omeprazole may be increased if taken together.

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine, even those not prescribed by a doctor.

This is very important as using more than one medicine at the same time may alter their

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effectiveness. If you have any questions or require further information, please talk to your doctor.

**Pregnancy and Breast-feeding:**

Use in pregnancy

Omeprazole has been shown to be safe for use during pregnancy.

Use in lactation

Omeprazole is excreted in breast milk but is not likely to affect the child at normal doses.

**3. How Omeprazole 40mg Powder for Solution for Infusion is given**

This medicine will always be given to you by a nurse or doctor. It is given by a drip over 20 – 30 minutes, once it has been made into a solution. If you require further information, ask the doctor or nurse who will be giving or who has given the medicine.

**Adults** The usual dose is 40mg omeprazole once daily, for up to 5 days. If you are given omeprazole to prevent acid aspiration (see Section 1), you will receive a single 40mg dose which will be completed one hour before surgery. The dose may be adjusted, to either lower or higher doses.

**Elderly or reduced kidney function** There is no requirement for patients with reduced kidney function or elderly patients to have a reduced dose.

**Reduced liver function** A reduced daily dose of 10mg - 20mg may be sufficient for patients with reduced liver function.

**Children** There is limited experience of the use of omeprazole in children.

**If you are given too much omeprazole**

Your doctor or nurse will make sure you are given the correct dose for you individually. If you have any questions or are worried about the dose being given, please ask your doctor or nurse.

**4. Possible side effects.**

Like all medicines, omeprazole may have side effects. However these are uncommon and are usually mild and temporary.

The following side effects may occur with the following frequencies:

**Common** – more than 1 in each 100 people taking omeprazole:

Headache, diarrhoea, constipation, stomach pain, feeling or being sick and flatulence (wind).

**Uncommon** – less than 1 in each 100 but more than 1 in each 1000 people taking omeprazole:

Dizziness, tingling sensations, light headedness, feeling faint, sleepiness, difficulty sleeping, sensations of spinning (vertigo), increased liver enzymes, rash, itching, urticaria (hives), generally feeling unwell.

**Rare** – less than 1 in each 1000 people taking omeprazole:

Confusion, agitation, aggression, depression, hallucinations (mainly in severely ill patients), breast enlargement in men, dry mouth, inflammation of the lining of the mouth and other similar tissues, thrush, changes in the levels of different types of blood cells, decline in brain function (in patients with severe liver disease), hepatitis, jaundice (yellowing of the skin and the whites of the eyes), liver failure, joint and muscle pain, muscle weakness, impotence (difficulty getting an erection), increased sensitivity to sunlight and sunbeds, skin rashes including severe conditions (Stevens-Johnson syndrome, toxic epidermal necrolysis), hair loss, allergic reactions including swelling of parts of the body, fever, difficulty breathing, kidney problems, anaphylactic shock, increased sweating, blurred vision, irreversible visual problems (in critically ill patients), taste disturbance and low sodium levels in the blood.

If anything else happens which is not mentioned in this leaflet, tell the doctor or nurse who has given you this medicine.

**5. Storing Omeprazole 40mg Powder for Solution for Infusion.**

The doctor or nurse responsible for giving you this medicine will ensure it has been reconstituted (dissolved into liquid) correctly before giving it to you. They will also check the following have been met:

Do not store above 25°C. Keep the vial in the outer carton.

Following reconstitution the product should be used immediately and not after 6 hours when stored at 25°C.

The product should not be used after the expiry date printed on the carton and vial.

If there are signs of damage to the vial or cap or if, after dilution, the solution is cloudy or contains particles, the product should not be used.

Date of preparation: March 2006

PL 10622/0232  
61601-P1




## Labels/Packaging

# OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION (OMEPRAZOLE SODIUM)

**PL 10622/0232**

## Carton mock-up Omeprazole 40mg Powder for Solution for Infusion

<p><b>FOR INTRAVENOUS USE</b></p> <ul style="list-style-type: none"> <li>• Each vial contains 40mg omeprazole (as omeprazole sodium)</li> <li>• Powder for solution for infusion.</li> <li>• To be administered as directed by the doctor.</li> <li>• Reconstitute with 100ml 5% glucose. Use immediately following dilution or within 6 hours when stored at 25°C.</li> <li>• For preparation and storage information see enclosed leaflet.</li> <li>• Contains sodium. Other ingredients are sodium hydroxide and disodium edetate.</li> <li>• Do not store above 25°C. Keep the vial in the outer carton.</li> <li>• For further information please read the enclosed leaflet.</li> </ul>	<p><b>Omeprazole</b> <b>40mg</b> <b>Powder for Solution for Infusion</b> <b>FOR INTRAVENOUS USE</b> Each vial contains 40mg omeprazole (as omeprazole sodium). 1 vial</p> <p>For single use only. Any remaining solution should be discarded.</p> <p style="text-align: center;"><b>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</b></p>	<div style="background-color: #800040; color: white; padding: 5px; text-align: center; font-weight: bold;">             Omeprazole <b>40mg</b> Powder for Solution for Infusion FOR INTRAVENOUS USE 1 vial         </div> <div style="text-align: center; padding: 10px;">  </div> <p>1 vial</p>	<p>MA Holder: PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB. PL 10622/0232</p> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="border: 1px solid black; padding: 2px;">BAR CODE</div> <div style="border: 1px solid black; padding: 2px;">POM ITEM CODE</div> </div>
<p>Batch: Expiry:</p>			

# OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION (OMEPRAZOLE SODIUM)

PL 10622/0232

Carton mock-up  
Omeprazole 40mg Powder for Solution for Infusion  
(5 vial pack)

<p><b>FOR INTRAVENOUS USE</b></p> <ul style="list-style-type: none"> <li>• Each vial contains 40mg omeprazole (as omeprazole sodium)</li> <li>• Powder for solution for infusion.</li> <li>• To be administered as directed by the doctor.</li> <li>• Reconstitute with 100ml 5% glucose. Use immediately following dilution or within 6 hours when stored at 25°C.</li> <li>• For preparation and storage information see enclosed leaflet.</li> <li>• Contains sodium. Other ingredients are sodium hydroxide and disodium edelate.</li> <li>• Do not store above 25°C. Keep the vial in the outer carton.</li> <li>• For further information please read the enclosed leaflet.</li> </ul> <p><b>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</b></p> <p>POM <small>from code</small></p> <p>BAR CODE</p>	<p><b>Omeprazole 40mg Powder for Solution for Infusion</b></p> <p><b>FOR INTRAVENOUS USE</b></p> <p>Each vial contains 40mg omeprazole (as omeprazole sodium).</p> <p>5 vials</p>	<p><b>Omeprazole 40mg Powder for Solution for Infusion</b></p> <p><b>FOR INTRAVENOUS USE</b></p> <p>Each vial contains 40mg omeprazole (as omeprazole sodium).</p> <p>5 vials</p> <p>For single use only. Any remaining solution should be discarded.</p> <p><b>MA Holder:</b> PLIVA Pharma Ltd. Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB. PL 10622/0232</p>
<p>Please note that this carton is not to scale.</p>		<p>Batch: Expiry:</p>







**OMEPRAZOLE 40MG POWDER FOR SOLUTION FOR INFUSION**  
**(OMEPRAZOLE SODIUM)**

**PL 10622/0232**

Label mock-up  
Omeprazole 40mg Infusion

**Omeprazole 40mg Powder for Solution for Infusion**  
FOR INTRAVENOUS USE. Contains 40mg omeprazole (as omeprazole sodium). Other ingredients: disodium edetate and sodium hydroxide. To be administered as directed by the doctor.  
Reconstitute with 100ml 5% glucose. Use immediately after reconstitution and dilution or within 6 hours when stored at 25°C. For single use only. Discard any remaining solution. Read the enclosed leaflet. Do not store above 25°C. Keep the vial in the outer carton.  
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.  Batch: \_\_\_\_\_  
MA Holder: PLIVA Pharma Ltd. PL 10622/0232.  Expiry: \_\_\_\_\_