Summary of Product's Characteristics

PantoAvenir I.V.

1. NAME OF THE MEDICINAL PRODUCT

PantoAvenir I.V.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains: Pantoprazole 40mg (as sodium sesquihydrate).

3. PHARMACEUTICAL FORM

Powder for Solution for Injection.
For Intravenous injection only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Duodenal ulcer
Ggastric ulcer
Moderate and severe reflux esophagitis
Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

PantoAvenir I.V. is for intravenous administration ONLY and must NOT be given by any other route.

The intravenous administration of PantoAvenir I.V. is recommended only if oral application is not appropriate.

Recommended dosage:

Duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis

The recommended intravenous dosage is one vial (40 mg pantoprazole) PantoAvenir I.V. per day.

Long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

Patients should start the treatment with a daily dose of 80 mg PantoAvenir I.V. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily.
A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg PantoAvenir I.V. is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.
The intravenous formula must be replaced by the oral formula as soon as it is clinically justified.

General instructions

A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution into the vial containing the dry substance. This solution may be administered directly or may be administered after mixing with 100 ml physiological sodium chloride solution, or 5% Glucose.

PantoAvenir I.V. should not be prepared or mixed with solvents other than those specified.

After preparation the solution must be used within 12 h.

The drug should be administered intravenously over 2 – 15 minutes.

As soon as oral therapy is possible, treatment with PantoAvenir I.V. should be discontinued and 40 mg Pantoprazole p.o. should be administered instead.

Pediatric patients

The experience in children is limited. Therefore, Pantoavenir I.V.40 mg powder for solution for injection is not recommended for use in patients below 18 years of age until further data become available.

4.3 Contra-indications

PantoAvenir I.V. should not be used in cases of known hypersensitivity to one of its components. Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see section 4.5).

4.4 Warnings and special precautions for use

The intravenous administration of PantoAvenir I.V. is recommended only if oral application is not appropriate.

Pantoprazole is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.
The reflux esophagitis diagnosis must be confirmed by means of an endoscopy.

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with pantoprazole may alleviate symptoms and delay diagnosis.
Further investigation is to be considered if symptoms persist despite adequate treatment.

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate for the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

The daily dose of 40 mg pantoprazole should not be exceeded in elderly patients or in those with impaired renal function.

In patients with severe liver impairment the daily dose has to be reduced to 20 mg pantoprazole. Furthermore, in these patients the liver enzymes should be monitored during PantoAvenir I.V. therapy. In case of a rise of the liver enzymes PantoAvenir I.V. should be discontinued.

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

This product contains less than 1 mmol of sodium (23 mg) per vial; that is, essentially "sodium free".

4.5 Interaction with other medicaments and other forms of interaction

Changes in absorption should be observed when drugs whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir (see section 4.3).

The active ingredient of PantoAvenir I.V. is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. No clinically significant interactions were, however, observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in prothrombin time / INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids

4.6 Pregnancy and lactation

Clinical experience in pregnant women is limited. ln animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.

4.7 Effects on ability to drive and use of machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Frequency Organ System	**Common (>1/100, <1/10)**	**Uncommon (>1/1,000, <1/100)**	**Rare (<1/1,000 >1/10,000)**	**Very rare (<1/10,000, incl. isolated reports**
Blood and lymphatic system				Leukopenia; Thrombocytopenia
Gastrointestinal disorders	Upper abdominal pain, Diarrhoea, Constipation, Flatulence	Nausea / vomiting	Dry mouth	
General disorders and administration site conditions				Injection site thrombophlebitis; peripheral edema
Hepatobiliary				Severe

disorders				hepatocellular damage leading to jaundice with or without hepatic failure
Immune system disorders				Anaphylactic reactions including anaphylactic shock
Investigations				Increased liver enzymes (transaminases, γ-GT); Elevated triglycerides; Increased body temperature
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Nervous system disorders	Headache	Dizziness; Disturbances in vision (blurred vision)		
Psychiatric disorders				Mental depression
Renal and urinary disorders				Interstitial nephritis
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus and skin rash		Urticaria; Angioedema; Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell-Syndrome; Photosensitivity

4.9 Overdose

There are no known symptoms of overdosage in man.
Doses up to 240 mg I.V. were administered over two minutes and were well tolerated.
In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Proton pump inhibitors

ATC code: A02B C02

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+/ K+-ATPase enzyme, i. e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

5.2 Pharmacokinetic properties

General pharmacokinetics

Volume of distribution is about 0.15 L/kg and clearance is about 0.1 1/h/kg. Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific activation of pantoprazole in the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are virtually linear after both oral and intravenous administration.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2 -3h), excretion is still rapid and thus accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-lifetime values increased to between 7 and 9 h and the AUC values increased by a factor of 5 -7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.
A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.
Children
Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2-16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In a 2-year carcinogenicity study in rats - which corresponds to lifetime treatment for rats - neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic treatment.

In the two-year studies an increased number of liver tumors was observed in rats and female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. From mutagenicity

studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects to the thyroid glands are expected.

Investigations revealed no evidence of impaired fertility or teratogenic effects.
Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate tetrasodium, mannitol, tromethamine.

6.2 Incompatibilities

PantoAvenir I.V. must not be prepared with any other solutions apart from the ones specified above (see 4-2).

6.3 Shelf life

PantoAvenir I.V. is stable over a period of 2 years.

The reconstituted solution must be used within 12 hours after preparation.

6.4 Special precautions for storage

Vial: Store at temperatures up to 25ºC
Keep the vial in the original carton.

6.5 Nature and contents of container

PantoAvenir I.V., as the dry substance in glass vial
1 vial in a carton box and 20 vials in a carton box.

6.6 Instructions for use/handling

A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution into the vial containing the dry substance. This solution may be administered directly or may be administered after mixing with 100 ml physiological sodium chloride solution, or 5% Glucose.

Reconstituted vial: the reconstituted solution is stable for 12 hours at 25ºC or 24 hours in a refrigerator (2 - 8ºC).

After reconstitution, the solution may be used within the following 12 or 24 hours, although 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 12 hours at not more than 25°C or 24 hours in a refrigerator (2 - 8ºC).

PantoAvenir I.V must not be prepared or mixed with solvents other than those stated.
The drug should be administered intravenously over 2 -15 minutes.

Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) has to be discarded.
The contents of the vial is intended for single use only.

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Laboratory Reig Jofre S.A., Barcelona, Spain

License Holder:
BioAvenir, Kibutz Glil Yam 46905

The format of this leaflet has been determined by the Ministry of Health and the content thereof has been checked and approved in March 2012.