

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/109/001

Case No: 2022433

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, Co. Cork, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Pantozol 40mg Powder for Solution for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **16/05/2008** until **15/05/2013**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantozol 40 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate).

3 PHARMACEUTICAL FORM

Powder for solution for injection.

A white to yellowish powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- duodenal ulcer
- gastric ulcer
- moderate and severe reflux esophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

4.2 Posology and method of administration

The intravenous administration of pantoprazole 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 40 mg pantoprazole (one vial) per day, given over a 2 to 15 minute period of time, for up to a week.

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

Patients should start their treatment with a daily dose of 80 mg pantoprazole 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 pantoprazole 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. Transition from pantoprazole i.v. to the oral formulation of pantoprazole should be performed 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. The medicinal product should be administered intravenously over 2-15 minutes.

After preparation the solution must be used within 12 hours stored at not more than 25 °C (see section 6.6).

Pantoprazole powder for solution for injection should not be manufactured or mixed with solvents other than those stated.

In most patients, freedom from symptoms is achieved rapidly.

As soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued.

Data are available on i.v. use for up to 7 days. Thereafter, oral pantoprazole treatment should be administered in compliance with the approved dosage regimen.

There is no information on the use of pantoprazole in children. Therefore pantoprazole i.v. should not be used in children.

4.3 Contraindications

Hypersensitivity to pantoprazole.

4.4 Special warnings and precautions for use

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate.

Pantoprazole is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

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

In patients requiring long term treatment such as Zollinger Ellison-Syndrome and other pathological hypersecretory conditions pantoprazole in common with acid-blocking medicines may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered if respective clinical symptoms are observed.

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 pantoprazole i.v. therapy. In case of a rise of the liver enzymes pantoprazole i.v. should be discontinued.

To date there has been no experience with treatment in children.

4.5 Interaction with other medicinal products and other forms of interaction

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

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other active ingredients 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 active ingredients 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 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

Pregnancy

Experience with pantoprazole in pregnant women is very limited. Limited experience with proton pump inhibitors as a class does not indicate an increased risk for major congenital malformations. In animal reproduction studies, signs of slight fetotoxicity were observed (see section 5.3). Pantoprazole should not be used unless clearly necessary..

Lactation

There is no information on the excretion of pantoprazole into human breast milk. Since potential risks to the child cannot be fully excluded, discontinuation of breastfeeding should be considered when treatment with pantoprazole is needed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Organ System	Frequency			
	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 disorders				Leukopenia; Thrombocytopenia
Gastrointestinal disorders	Upper abdominal pain; Diarrhoea; Constipation; Flatulence	Nausea/Vomiting	Dry mouth	
General disorders and administration site conditions				Injection site thrombophlebitis; Peripheral oedema
Hepatobiliary disorders				Severe 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 sub-cutaneous 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. As pantoprazole is extensively protein bound, it is not readily dialysable. Apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Proton Pump Inhibitors. ATC code: A02BC02

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 l/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 (2-3 h), 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 C_{\max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

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.

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

In a 2-year carcinogenicity study in 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 humans under chronic treatment with proton pump inhibitors the formation of gastric tumors has not been reported thus far, but the information is still limited.

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. This rodent-specific mechanism of carcinogenesis is considered without relevance for the treatment of humans with pantoprazole. A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). 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, but a slight reduction in skeletal ossification was observed in rats at or close to clinical levels of exposure.

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

Not applicable.

6.2 Incompatibilities

This medicinal product should not be manufactured or mixed with solvents other than those stated in sections 4.2 and 6.6.

6.3 Shelf Life

1 year.

After reconstitution (and dilution): Do not store above 25°C and use within 12 hours.

6.4 Special precautions for storage

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

For storage conditions of the reconstituted (and diluted) medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I glass vial, closed with a red rubber stopper and sealed by aluminium cap.

Packs of 1, 5, 10 and 20 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

After preparation the solution must be used within 12 hours. 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.

Pantoprazole powder for solution for injection should not be manufactured or mixed with solvents other than those stated.

The medicinal product 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 for single use only.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co.Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/109/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16th May 2008.

10 DATE OF REVISION OF THE TEXT