

PANTOMAX® 40 mg gastro-resistant tablets SAJA PHARMA

Pantoprazole

1. NAME OF THE MEDICINAL PRODUCT

Pantomax® 40 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole (as sodium sesquihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Yellow, oval biconvex enteric-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Moderate & severe cases of inflammation of the esophagus (Reflux oesophagitis).
- Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcer.

4.2 Posology and method of administration

Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Recommended dose

Reflux oesophagitis

One tablet of Pantomax per day. In individual cases the dose may be doubled (increase to 2 tablets Pantomax daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults

Eradication of *H. pylori* in combination with two appropriate antibiotics

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination

therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

- a) twice daily one tablet Pantomax + twice daily 1000 mg amoxicillin + twice daily 500 mg clarithromycin
- b) twice daily one tablet Pantomax + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole) + twice daily 250 - 500 mg clarithromycin
- c) twice daily one tablet Pantomax + twice daily 1000 mg amoxicillin + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second Pantomax tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *H. pylori*, the following dose guidelines apply for Pantomax monotherapy:

Treatment of gastric ulcer

One tablet of Pantomax per day. In individual cases the dose may be doubled (increase to 2 tablets Pantomax daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Treatment of duodenal ulcer

One tablet of Pantomax per day. In individual cases

the dose may be doubled (increase to 2 tablets Pantomax daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Special populations

Children below 12 years of age

Pantomax is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic Impairment

A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantomax must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Pantomax in combination treatment of these patients (see section 4.4).

Renal Impairment

No dose adjustment is necessary in patients with impaired renal function. Pantomax must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Pantomax in combination treatment for these patients.

Elderly

No dose adjustment is necessary in elderly patients.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients.

4.4 Special warnings and precautions for use

Hepatic Impairment

In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued (see section 4.2).

Co-administration with NSAIDs

The use of Pantomax 20 mg as a preventive of

gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

In presence of alarm symptoms

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.

Co-administration with atazanavir

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). 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. A pantoprazole dose of 20 mg per day should not be exceeded.

Influence on vitamin B12 absorption

Pantoprazole, 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 or if respective clinical symptoms are observed.

Long term treatment

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal infections caused by bacteria

Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract.

Treatment with Pantomax may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on the absorption of other medicinal products

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV medications (atazanavir)

Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors, might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)

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

Other interactions studies

Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive

containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol), or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantomax should not be used during pregnancy, unless clearly necessary.

Lactation

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantomax should be made taking into account the benefit of breast-feeding to the child, and the benefit of Pantomax therapy to women.

4.7 Effects on ability to drive and use machines

Adverse drug reactions, such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and

headache, both occurring in approximately 1% of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

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

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. See Table.

4.9 Overdose

There are no known symptoms of overdose in man.

Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of an overdose with clinical signs of intoxication, 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

Mechanism of action

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of 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. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors

and H₂ receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases 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, it can inhibit 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.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole is linear after both oral and intravenous administration.

The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Uncommon	Rare	Very rare	Not known
System Organ Class			
Blood and lymphatic system disorders			
	Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			
	Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			
	Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia
Psychiatric disorders			
Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders			
Headache; Dizziness	Taste disorders		
Eye disorders			
	Disturbances in vision / blurred vision		
Gastrointestinal disorders			
Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders			
Liver enzymes increased (transaminases, γ -GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders			
Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multi-forme; Photosensitivity
Musculoskeletal and connective tissue disorders			
	Arthralgia; Myalgia		
Renal and urinary disorders			
			Interstitial nephritis
Reproductive system and breast disorders			
	Gynaecomastia		
General disorders and administration site conditions			
Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

the lag-time will be increased by concomitant food intake.

Distribution

Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15l/kg.

Elimination

The substance is almost exclusively metabolized in

the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway includes oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton

pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is 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 hours) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects
Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including 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-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3 - 5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years

AUC and C_{max} were in the range of corresponding values in adults.

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

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 harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg.

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

Mannitol, Crospovidone, Sodium Carbonate Anhydrous, Hyrromellose, Calcium Stearate, Opadry, Acryl eze.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package

6.5 Nature and contents of container

How supplied

Packs of 15, 30 enteric coated tablets: Each enteric coated tablet contains Pantoprazole Sodium Sesquihydrate equivalent to 40 mg Pantoprazole.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SAJA Pharmaceuticals

Saudi Arabian Japanese pharmaceutical company limited

Jeddah – Saudi Arabia

For more information, please contact

Saudi Arabian Japanese pharmaceutical company limited

Jeddah – Saudi Arabia

P.O. Box: 42600, Jeddah 21551, KSA

Tel: + 966 2 645 0303

www.sjaonline.net

8. MARKETING AUTHORIZATION NUMBER

Pantomax 40 mg 15 tab 27/370/06

Pantomax 40 mg 30 tab 26/370/06

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Pantomax 40 mg 15 tab 01/04/1427

Pantomax 40 mg 30 tab 02/04/1427

10. DATE OF REVISION OF THE TEXT

July 2012