
1. NAME OF THE MEDICINAL PRODUCT

Nolpaza® 40 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole as 45.10 mg pantoprazole sodium sesquihydrate.

Excipient:
Each gastro-resistant tablet contains 36 mg sorbitol (E420).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Light yellowish brown, oval, slightly biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents 12 years of age and above
- Reflux oesophagitis

Adults
- Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcers.
- Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years of age and above

Reflux oesophagitis
One Nolpaza 40 mg gastro-resistant tablet per day. In individual cases, the dose may be doubled (increase to 2 Nolpaza 40 mg gastro-resistant tablets 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 Nolpaza 40 mg gastro-resistant tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) twice daily one Nolpaza 40 mg gastro-resistant tablet
+ twice daily 400–500 mg metronidazole (or 500 mg tinidazole)
+ twice daily 250–500 mg clarithromycin

c) twice daily one Nolpaza 40 mg gastro-resistant tablet
+ 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 Nolpaza 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 Nolpaza monotherapy:

Treatment of gastric ulcer
One Nolpaza 40 mg gastro-resistant tablet per day. In individual cases, the dose may be doubled (increase to 2 Nolpaza 40 mg gastro-resistant tablets 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 Nolpaza 40 mg gastro-resistant tablet per day. In individual cases, the dose may be doubled (increase to 2 Nolpaza 40 mg gastro-resistant tablets 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.

Zollinger-Ellison syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions, patients should start their treatment with a daily dose of 80 mg (2 Nolpaza 40 mg gastro-resistant tablets 40 mg). Thereafter, the dose 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 dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.
Treatment duration in Zollinger-Ellison syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Special populations

Hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment. Nolpaza must not be used in combination with antibiotics 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 Nolpaza 40 mg gastro-resistant tablets in combination treatment of these patients (see section 4.4).

Renal impairment
No dose adjustment is necessary in patients with impaired renal function. Nolpaza must not be used in combination with antibiotics for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Nolpaza 40 mg gastro-resistant tablets in combination treatment of these patients.

Elderly
No dose adjustment is necessary in elderly patients.

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

Method of administration
The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

4.3 Contraindications

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

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).

Combination therapy
In the case of combination therapy for eradication of *H. pylori*, the summaries of product characteristics of the respective medicinal products should be observed.

Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Influence on vitamin B_{12} absorption
Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} (cyanocobalamin) 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
Treatment with Nolpaza may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella,Campylobacter and C.difficile*.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia, such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia, can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Hip, wrist or spine fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Nolpaza. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Nolpaza treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Nolpaza contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH-Dependent Absorption Pharmacokinetics
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral availability, e.g. some azole antifungals (ketoconazole, itraconazole, posaconazole) and other medicines such as erlotinib.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).
If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interaction studies
Pantoprazole is extensively metabolised 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 metabolised with these pathways, such as carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not affect 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 administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19:
Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (*Hypericum perforatum*) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of Nolpaza.
Studies in animals have shown reproductive toxicity (see section 5.3). Nolpaza should not be used during pregnancy unless clearly necessary.

Breastfeeding
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 Nolpaza should be made taking into account the benefit of breast-feeding to the child and the benefit of Nolpaza therapy to women.

Fertility
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

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

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.

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

Frequency / System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			agranulocytosis	thrombocytopenia; leukopenia; pancytopennia	
Immune system disorders			hypersenstivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			hyperlipidaemias and lipid increases (triglycerides, cholesterol); weight changes		hyponatraemia; hypomagnesaemia *(see section 4.4);* hypocalcaemia in association with hypomagnesaemia; hypokalaemia
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		parasthesia
Eye disorders			disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	diarrhoea; nausea/vomiting; abdominal distension and bloating; constipation; dry mouth; abdominal pain and discomfort			Microscopic colitis
Hepatobiliary disorders		liver enzymes increased (transaminases, γ-GT)	bilirubin increased		hepatocellular injury; jaundice; hepatocellular failure

Skin and subcutaneous tissue disorders		rash/exanthema/ eruption; pruritus	urticaria; angioedema		Stevens-Johnson syndrome; Lyell's syndrome; erythema multiforme; photosensitivity; subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders		hip, wrist or spine fracture *(see section 4.4)*	arthralgia; myalgia		muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders					interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			gynaecomastia		
General disorders and administration site conditions		asthenia; fatigue and malaise	body temperature increased; oedema peripheral		

4.9 Overdose

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of 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: Drugs for acid related disorders, 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 H_2 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An influence of long-term (exceeding one year) treatment with pantoprazole on endocrine parameters of the thyroid cannot be completely ruled out 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 40 mg oral dose. On average at about 2.5 h p.a. the maximum plasma concentrations of about 2–3 µg/ml are achieved and these values remain constant after multiple administration. The pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are 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 the AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

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

Metabolism and elimination
Pantoprazole is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4. The terminal half-life is about 1 hour and clearance about 0.1 l/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 dialysed. Although the main metabolite has a moderately delayed half-life (2–3 h), excretion is still rapid and thus accumulation does not occur.

In patients with liver cirrhosis (classes A and B according to Child), the half-life values increased to between 7 and 9 h, the AUC values increased by a factor of 5–7 and the maximum plasma concentration increased by a factor of 1.5 compared to healthy subjects after 40 mg oral dose.

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, the 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. The 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 tumours 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 of pantoprazole (200 mg/kg) in a two-year study. 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 foetotoxicity 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, the concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Manitol
Crospovidone
Anhydrous sodium carbonate
Sorbitol
Calcium stearate
Hypromellose
Povidone
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Propylene glycol
Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent (sodium laurilsulfate, polysorbate 80)
Talc
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30°C. Store in original packaging in order to protect from moisture.

6.5 Nature and contents of container

Blisters: 14, 28 or 56 tablets (1, 2 or 4 blister packs of 14 tablets), in a box.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT