

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nolpacid 20 mg gastro-resistant tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablets contains 20 mg pantoprazole as pantoprazole sodium sesquihydrate.

Excipient with known effect:

- sorbitol (E420): 18 mg/tablet

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Gastro-resistant tablets are light yellowish brown, oval (3 mm x 9 mm), slightly biconvex film-coated tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

### 4.2 Posology and method of administration

#### Posology

The recommended dose is 20 mg pantoprazole (one tablet) per day.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms. Once complete relief of symptoms has occurred, treatment should be discontinued. The treatment should not exceed 4 weeks without consulting a doctor.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

#### *Special populations*

No dose adjustment is necessary in elderly patients or in those with impaired renal or liver function.

#### *Paediatric population*

Nolpacid is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

#### Method of administration

Nolpacid 20 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

#### 4.4 Special warnings and precautions for use

Patients should be instructed to consult a doctor if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, since pantoprazole may alleviate symptoms and delay diagnosis of a severe condition. In these cases, malignancy should be excluded.
- They have had previous gastric ulcer or gastrointestinal surgery.
- They are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice, hepatic impairment, or liver disease.
- They have any other serious disease affecting general well-being.
- They are aged over 55 years with new or recently changed symptoms. Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor. Patients should not take another proton pump inhibitor or H<sub>2</sub> antagonist concomitantly. Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test. Patients should be advised that the tablets are not intended to provide immediate relief. Patients may start to experience symptomatic relief after approximately one day of treatment with pantoprazole, but it might be necessary to take it for 7 days to achieve complete heartburn control. Patients should not take pantoprazole as a preventive medicinal product. Gastrointestinal infections caused by bacteria 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 medicinal products leads to a slightly increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter*, or *C. difficile*.

##### Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported in association with pantoprazole with frequency not known (see section 4.8).

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, pantoprazole should be withdrawn immediately and an alternative treatment considered.

##### 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 Nolpacid. 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, Nolpacid 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.

This medicinal product is intended for short-term use (up to 4 weeks) only (Refer to section 4.2). Patients should be warned about additional risks with long-term use of the medicinal products and the need for prescription and regular surveillance should be emphasized.

The following additional risks are considered relevant for long-term use:

##### Influence on vitamin B<sub>12</sub> absorption:

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B<sub>12</sub> (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B<sub>12</sub> absorption on long-term therapy or if respective clinical symptoms are observed.

##### Bone 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 older people or in 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.

#### Hypomagnesaemia:

Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (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. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

#### Nolpacid contains sorbitol and sodium.

This medicine contains 18 mg sorbitol in each tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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

#### Medical products with pH dependent absorption pharmacokinetics

Nolpacid may reduce the absorption of active substances whose bioavailability is dependent on the gastric pH (e.g. ketoconazole).

#### HIV protease inhibitors:

Co-administration of pantoprazole is contraindicated with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability (see section 4.3).

#### 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.

#### 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 interactions studies

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. Interaction studies with carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions. However, an interaction of pantoprazole with other substances which are metabolised by the same enzyme system cannot be excluded.

There were no interactions with concomitantly administered antacids.

#### Drug-laboratory test interactions

There have been reports of false-positive results in some urine screening tests for tetrahydrocannabinol (THC) in patients receiving pantoprazole. An alternative confirmatory method should be considered to verify positive results.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity. Preclinical studies revealed no evidence of impaired fertility or teratogenic effects (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy.

### Breast-feeding

Pantoprazole/metabolites have been identified in human milk. The effect of pantoprazole on newborns/infants is unknown. Nolpacid should not be used during breast-feeding.

### 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

Nolpacid has no or negligible influence on the ability to drive and use machines. However adverse reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or use machines.

## 4.8 Undesirable effects

### Summary of the safety profile

Approximately 5% of patients can be expected to experience adverse reactions.

### Tabulated list of adverse reactions

The following adverse reactions have been reported with pantoprazole.

Within the following table, adverse reactions are ranked under the MedDRA 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)

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*

<b>Frequency</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>	<b>Not known</b>
<b>System</b>					
<b>Organ Class</b>					
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leucopenia; 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, Hypocalcaemia <sup>(1)</sup> , Hypokalaemia <sup>(1)</sup>

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		Paraesthesia
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, $\gamma$ -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; (TEN); Drug reaction with eosinophilia and systemic symptoms (DRESS); Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal, connective tissue disorders		Fracture of wrist, hip and spine	Arthralgia; Myalgia		
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (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		<sup>(1)</sup> Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)

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#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: [www.hpra.ie](http://www.hpra.ie).

#### **4.9 Overdose**

Doses 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 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, a cyclic sulphenamide, 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 heartburn and acid reflux symptoms is achieved in 1 week. 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 receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance 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.

### Clinical efficacy and safety

In a retrospective analysis of 17 studies in 5960 patients with gastro-oesophageal reflux disease (GORD) who were treated with 20 mg pantoprazole monotherapy, the symptoms associated with acid reflux e.g. heartburn and acid regurgitation were evaluated according to a standardised methodology. Studies selected had to have at least one acid reflux symptom recording point at 2 weeks. GORD diagnosis in these studies was based on endoscopic assessment, with the exception of one study in which the inclusion of the patients was based on symptomatology alone.

In these studies, the percentage of patients experiencing complete relief from heartburn after 7 days was between 54.0% and 80.6% in the pantoprazole group. After 14 and 28 days, complete heartburn relief was experienced in 62.9% to 88.6% and 68.1% to 92.3% of the patients, respectively.

For the complete relief from acid regurgitation, similar results were obtained as for heartburn. After 7 days the percentage of patients experiencing complete relief from acid regurgitation was between 61.5% and 84.4%, after 14 days between 67.7% and 90.4%, and after 28 days between 75.2% and 94.5%, respectively.

Pantoprazole was consistently shown to be superior to placebo and H2RA and non-inferior to other PPIs. Acid-reflux symptom relief rates were largely independent of the initial GORD stage.

## 5.2 Pharmacokinetic properties

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.

### Absorption

Pantoprazole is completely and rapidly absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77 %. On average, at about 2.0 h - 2.5 h post administration ( $t_{max}$ ) of a single 20 mg oral dose, the maximum serum concentrations ( $C_{max}$ ) of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Concomitant intake of food had no influence on bioavailability (AUC or  $C_{max}$ ), but increased the variability of the lag-time ( $t_{lag}$ ).

### Distribution

Volume of distribution is about 0.15 l/kg and serum protein binding is about 98%.

### Biotransformation

Pantoprazole is almost exclusively metabolized in the liver.

### Elimination

Clearance is about 0.1 l/h/kg, and terminal half-life ( $t_{1/2}$ ) about 1 h. There were a few cases of subjects with delayed elimination. Due to the specific binding of pantoprazole to the proton pumps within 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 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.

### Special populations

#### Renal impairment

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including patients on dialysis, which removes only negligible amounts of pantoprazole). As with healthy subjects, the half-life of pantoprazole is short. Although the main metabolite has a longer half-life (2-3h), excretion is still rapid and thus accumulation does not occur.

#### Hepatic impairment

After administration of pantoprazole to patients with liver impairment (Child-Pugh classes A, B and C) the half-life values increased to between 3 and 7 h and the AUC values increased by a factor of 3-6, whereas the  $C_{max}$  only increased slightly by a factor of 1.3 compared with healthy subjects.

#### Elderly

The slight increase in AUC and  $C_{max}$  in elderly volunteers compared with younger subjects was not clinically relevant.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the 2-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. 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 2-year rodent studies an increased number of liver tumors was observed in rats (in one rat study only) 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) in one 2-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 side effects on the thyroid glands are expected.

In a peri-postnatal rat reproduction study designed to assess bone development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were observed at exposures ( $C_{max}$ ) approximately 2x the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups and body weights were also trending toward reversibility after a drug-free recovery period. The increased mortality has only been reported in pre-weaning rat pups (up to 21 days age) which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous peripostnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study.

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 fetus is increased shortly before birth.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

mannitol  
crospovidone (type B)  
sodium carbonate  
sorbitol (E420)  
calcium stearate

#### Film coating:

hypromellose  
povidone  
titanium dioxide (E 171)  
iron oxide, yellow (E 172)  
propylene glycol  
methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent  
sodium laurilsulfate  
polysorbate 80  
macrogol 6000  
talc

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

5 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture.  
This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

Blister pack (OPA/Alu/PVC-Alu foil): 7 gastro-resistant tablets (1 blister pack of 7 tablets), in a box.  
Blister pack (OPA/Alu/PVC-Alu foil): 14 gastro-resistant tablets (2 blister packs of 7 tablets or 1 blister pack of 14 tablets), in a box.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7 MARKETING AUTHORISATION HOLDER

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

## 8 MARKETING AUTHORISATION NUMBER

PA1347/032/001



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

Date of First Authorisation: 25<sup>th</sup> November 2013

Date of last renewal: 17<sup>th</sup> October 2018

**10 DATE OF REVISION OF THE TEXT**

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