# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Panto-Denk 20

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: pantoprazole

Each gastro-resistant tablet contains 20 mg pantoprazole, equivalent to 22.6 mg pantoprazole sodium sesquihydrate.

Excipients with known effect:
Each gastro-resistant tablet contains 38.425 mg maltitol, less than 1 mmol sodium (23 mg) and soya oil.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Yellow, oval gastro-resistant tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Panto-Denk 20 is indicated for use in adults and adolescents 12 years of age and above for:

- symptomatic gastro-oesophageal reflux disease
- long-term management and prevention of relapse in reflux oesophagitis.

Panto-Denk 20 is indicated for use in adults for:

- prevention of gastroduodenal ulcers induced by non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

### 4.2 Posology and method of administration

**Posology**

Adults and adolescents aged 12 years and above
*Symptomatic gastro-oesophageal reflux disease*
The recommended oral dose is one gastro-resistant tablet (20 mg pantoprazole) per day. Symptom relief is generally accomplished within 2-4 weeks. If this is not sufficient, symptom relief will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, taking one tablet when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

*Long-term management and prevention of relapse in reflux oesophagitis*
For long-term management, a maintenance dose of one gastro-resistant tablet (20 mg pantoprazole) per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg is available for this case. After healing of the relapse the dose can be reduced again to 20 mg pantoprazole.

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.
The recommended oral dose is one gastro-resistant tablet (20 mg pantoprazole) per day.

Special populations

*Patients with hepatic impairment*
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4).

*Patients with renal impairment*
No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

*Elderly people*
No dose adjustment is necessary in elderly patients (see section 5.2).

*Paediatric population*
Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group (see section 5.2).

**Method of administration**

Oral use. 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, soya, peanuts or to any of the excipients listed in section 6.1.

## 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 pantoprazole 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.

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 pre-

sent, 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 resorption 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 $B_{12}$ 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 pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* and *C. difficile*.

Hypomagnesaemia
Severe hypomagnesaemia has been rarely 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. 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.

Bone fractures
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.

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 pantoprazole. 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, pantoprazole 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 medicine contains maltitol and sodium.**
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

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 such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which resorption 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 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 medicinal products 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.
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 by 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 300-1,000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of pantoprazole. Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of pantoprazole during pregnancy.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from pantoprazole therapy should take into account the benefit of breast-feeding for the child, and the benefit of pantoprazole 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

Pantoprazole has no or negligible influence on the 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).

Table 1 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).

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, 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 (see section 4.4); Hypocalcaemia[(1)] Hypokalaemia[(1)] |
| Psychiatric disorders | | Sleep disorders | Depression (and all aggravations) | Disorientation (and all aggravations) | Hallucination; Confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of preexistence) |
| 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 |

| Frequency / System organ class | common | uncommon | rare | very rare | not known |
|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | | Rash/exanthema/eruption; Pruritus | Urticaria; Angioedema | | Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity, Subacute cutaneous lupus erythematosus (see section 4.4); Drug reaction with eosinophilia and systemic symptoms (DRESS) |
| Musculoskeletal and connective tissue disorders | | Fracture of the hip, wrist or spine (see section 4.4) | Arthralgia; Myalgia | | Muscle spasm[(2)] |
| 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 | | |

[(1)] Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)
[(2)] Muscle spasm as a consequence of electrolyte disturbance

**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 the national reporting system.

## 4.9 Overdose

There are no known symptoms of overdose in humans.
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: Drugs for acid related disorders, proton pump inhibitors; ATC code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits gastric acid secretion by specifically reacting with the proton pumps of parietal cells.

Pantoprazole is converted to its active form in the acid compartment of parietal cells, where it inhibits $H^+/K^+$-ATPase, i.e. the final stage of acid production in the stomach. Inhibition is dose-dependent and acts on both basal and stimulated gastric acid secretion. In most patients, symptomatic relief is achieved within 2 weeks. As with other proton pump inhibitors and $H_2$-receptor blockers, gastric acid is reduced by treatment with pantoprazole, leading to a rise in gastrin levels in proportion to acid reduction. The rise in gastrin levels is reversible. As pantoprazole binds to the enzyme distal to the receptor level, it can influence acid secretion irrespectively of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether pantoprazole is administered orally or intravenously.

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.

Pharmacodynamic effects
Fasting levels of gastrin rise during pantoprazole treatment. In short-term use, they do not usually exceed the upper threshold value. During long-term treatment, gastrin levels double in most cases. However, an excessive increase occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine cells (ECL = enterochromaffin-like) in the stomach is observed (simple to adenomatous hyperplasia) in a minority of cases during long-term treatment. 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.

Based on data from animal studies, effects on endocrine thyroid and liver enzyme parameters cannot be excluded in long-term treatment with pantoprazole beyond one year.

### 5.2 Pharmacokinetic properties

Absorption
Pantoprazole is rapidly absorbed. Full active substance levels are achieved even after single oral administration of 20 mg pantoprazole. On average, the maximum serum concentration of approximately 1-1.5 µg/ml is reached after about 2.0 – 2.5 hours post-dose and remains constant even after multiple administration.
The pharmacokinetic characteristics after single and repeated administration do not differ. Within the dose range of 10-80 mg, pantoprazole has virtually linear kinetics both after oral and intravenous administration.
For the absolute bioavailability of the tablet, values of around 77% were found. No effect on AUC, peak serum concentration and hence bioavailability was found from concomitantly ingested food. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution
The serum protein binding of pantoprazole is around 98%. The volume of distribution is approximately 0.15 l/kg.

Biotransformation
Pantoprazole is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4.

Elimination
Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. In a few cases, subjects with delayed elimination have been observed. Due to the specific activation of pantoprazole in the parietal cell, the elimination half-life does not correlate to the much longer duration of action (inhibition of acid secretion).

Most of the metabolites (about 80%) are renally excreted, with the remainder via the faeces. In both serum and urine, the main metabolite is desmethyl pantoprazole, which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is only negligibly longer than that of pantoprazole.

Special populations
*Poor metabolisers*
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.

*Renal impairment*
No dose reduction is required when administering pantoprazole to patients with impaired renal function (including dialysis patients). As in healthy subjects, the half-life is short. Pantoprazole is dialysed only to a very minor extent. Although the main metabolite has a moderately prolonged half-life (2 - 3 h), no accumulation occurs as excretion is nevertheless rapid.

*Hepatic impairment*
Although for patients with liver cirrhosis (classes A and B according to Child), the half-life is prolonged to values between 3-6 h and AUC values are increased by a factor of 3-5, the maximum serum concentration only increases slightly by a factor of 1.3 compared with healthy subjects.

*Elderly people*
A slight increase in AUC and $C_{max}$ in elderly versus younger subjects has likewise no clinical relevance.

*Paediatric population*
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

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

In a 2-year study to investigate carcinogenic potential in rats, neuroendocrine neoplasms were found. Furthermore, squamous cell papillomas occurred in one study in the forestomach of rats. The mechanism behind the development of gastric carcinoids due to substituted benzimidazoles has been carefully investigated and allows the conclusion that an indirect mechanism is at work, as a result of highly elevated serum gastrin levels in rats during chronic high-dose treatment. In rats and female mice, an increased number of hepatic tumours were observed in the two-year studies, which is interpreted as being the result of the high metabolic rate of pantoprazole in the liver.

A slight increase in neoplastic thyroid changes was observed in the highest dose group (200 mg/kg) in rats. Occurrence of these neoplasms is related to pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. On account of the low therapeutic dose in humans, no undesirable effects on the thyroid gland 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 peri-postnatal 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 foetus is increased shortly before birth.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Maltitol
Crospovidone
Carmellose sodium
Sodium carbonate
Calcium stearate
Poly(vinyl alcohol)
Talc
Titanium dioxide
Macrogol 3350
Lecithin from soya beans
Iron oxide yellow
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store below 30 °C.

### 6.5 Nature and contents of container

Aluminium/aluminium blisters

Pack size: 28 gastro-resistant tablets

### 6.6 Special precautions for disposal and other handling

No special requirements

## 7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

## 8. MARKETING AUTHORISATION NUMBER IN GERMANY

78671.00.00

## 9. DATE OF FIRST AUTHORISATION IN GERMANY

25.11.2009

## 10. DATE OF REVISION OF THE TEXT

02/2022

## 11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription