SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANDEV 20 mg Enteric Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Pantoprazole 20 mg (as 22.56 mg pantoprazole sodium sesquihydrate)

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric Coated Tablet
Pale yellow, oblong film coated tablets with homogenous appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents 12 years of age and above:
It is indicated in:
- In the treatment of symptomatic gastro-esophageal reflux disease.
- Long-term management and prevention of relapse in reflux esophagitis

Adults:
It is indicated in:
- 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 (see section 4.4).

4.2 Posology and method of administration

Posology/frequency and duration of administration:

Adults and adolescents 12 years of age and above:
Symptomatic Gastro-esophageal reflux disease
The recommended oral dose is 1 PANDEV 20 mg tablet 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 esophagitis
For long-term management, a maintenance dose of 1 PANDEV 20 mg tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg tablet is available for this case. After healing of the relapse the dose can be reduced again to Pantoprazole 20 mg tablet.

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 PANDEV 20 mg tablet per day.

Method of administration:
Taken orally.
PANDEV should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Additional information on special populations:

Renal Impairment:
No dose adjustment is necessary in patients with impaired renal function.

Hepatic Impairment:
A daily dose of 20 mg pantoprazole (1 PANDEV 20 mg) should not be exceeded in patients with severe liver impairment.

Pediatric Population:
Pantoprazole is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in this age group (see section 5.2).

Geriatric Population:
No dose adjustment is necessary in the elderly (see section 5.2)

4.3 Contraindications
PANDEV is contraindicated in patients who are hypersensitive to its active substance, substituted benzimidazoles, or to any ingredient in the formulation.

4.4 Special warnings and precautions for use

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

Co-administration with NSAIDs
The use of PANDEV 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, hematemesis, anemia or melena) 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 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
Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Bone fracture:
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
The risk of fracture was increased in patients who received high-dose, defined as multiple doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
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.

Hypomagnesemia:
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs like pantoprazole for at least three months, and in most cases after a year of therapy. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia can occur. In most patients, treatment of hypomagnesaemia required 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.

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 healthcare 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.

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, PANDEV may interfere with absorption of drugs where gastric pH is an important determinant of the bioavailability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other drugs 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 inhibitors may need to be adjusted.

Coumarin anticoagulants (phenprocoumon and 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 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 metabolized 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.

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.

Additional information on special populations:
No interaction study on special populations has been conducted.

4.6 Fertility, pregnancy and lactation

General principles:
Pregnancy category is B.

Women of child-bearing potential/Contraception
There are no clinically significant data obtained from specific tests conducted with oral contraceptives containing levonorgestrel and etinyl estradiol (see section 4.5).

Pregnancy
Limited data on pregnant women (between 300-1000 pregnancy outcomes) indicate no adverse effects on fetus/newborn (malformation or feto/neonatal toxicity) of Pantoprazole. No significant epidemiological data has been found to date.
Animal studies have shown reproductive toxicity (see section 5.3).
The potential risk for humans is unknown.
As a precautionary measure, it is preferable to avoid the use of Pantoprazole during pregnancy.

Breastfeeding
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 for the woman.

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 are expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhea and headache, both occurring in approximately 1% of patients.
According to the organ system classification, the frequency of adverse reactions is classified as indicated below: 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/ Organ system	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia, Leucopenia, Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutritional disorders			Hyperlipidemia and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatremia, Hypomagnesaemia (see section 4.4), Hypocalcemia[1], Hypokalemia
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 the case of pre-existence)
Nervous system disorders		Dizziness, Headache	Taste disorder		Parasthesia
Ophthalmic disorders			Disturbances in vision/ blurred vision		
Gastrointestinal Disorders	Fundic gland polyps (benign)	Diarrhea, Nausea/ vomiting, Abdominal pain and discomfort, Constipation, Dry mouth, Abdominal pain			

		and discomfort			
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 syndrome, Erythema multiforme, Photosensitivity Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal, connective tissue disorders		Fractures of the wrist, hip and spine (see section 4.4)	Arthralgia, Myalgia		Muscle spasm[2]
Renal and urinary tract disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynecomasty		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased, Edema peripheral		

[1.] Hypocalcemia in association with hypomagnesemia
[2.] Muscle spasm as a consequence of electrolyte disturbance

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 to Turkey Pharmacovigilance Centre (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose

There are no known symptoms of overdose in humans.
Single doses of up to 240 mg IV administered over 2 minutes have been administered and were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialyzable.
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: Proton pump inhibitors
ATC code: A02BC02

Mechanism of action:
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid (gastric acid) in the stomach by specific blockade of the proton pumps in the acid-secretory parietal cells.
Pantoprazole is converted into its active form in the acidic environment of the parietal cells where it inhibits the H^+, K^+-ATPase enzyme, 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 antagonists, treatment with pantoprazole causes a reduced acidity in the stomach and thereby leading to an increase in gastrin in proportion to the reduction in the acidity. The increase in gastrin is reversible.
Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion irrespective of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

Pharmacodynamic effects:
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.

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.

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and possibly also *Clostridium difficile* in hospital patients.

5.2 Pharmacokinetic properties

General specifications
Absorption
Pantoprazole is rapidly absorbed and the maximum plasma level is achieved even after a single 40

mg oral dose. On average at about 2.5 h p.a. maximum serum concentrations of about 2 to 3 mcg/ml are achieved, and these values remain constant after multiple administration.
Pharmacokinetics do not vary after single or repeated administration.
The absolute bioavailability from tablets is about 77%. Concomitant intake of food has no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution
Pantaoprazole is 98% bound to serum proteins. Volume of distribution is approximately 0.15 L/kg.

Biotransformation
The substance is almost completely metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 followed by sulphate conjugation and other metabolic pathways which include oxidation by CYP3A4.

Elimination
The terminal half-life is about 1 h and the clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. As pantoprazole specifically binds 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 feces. 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.

Linearity/non-linearity
The pharmacokinetics of pantoprazole does not change upon either single or repeated dosing. Pantoprazole shows linear plasma kinetics within the dose-range of 10-80 mg after both IV and oral administration.

Characteristics in patients

Poor metabolizers:
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 catalyzed 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 in patients with renal impairment or in patients undergoing hemodialysis. As with healthy subjects, pantoprazole's half-life is short and only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half life (2-3 h), excretion is still rapid and thus any accumulation does not occur.

Hepatic impairment:
Although in patients with liver cirrhosis (classes A and B according to Child) the half-life increased

to between 7 and 9 h and the AUC increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Geriatric population:
A slight increase in AUC and C_{max} occurred in elderly volunteers when compared with younger volunteers is also not clinically relevant.

Pediatric population:
Following administration of single IV doses of 0.8 or 1.6 mg/kg pantoprazole to children aged between 2 and 16 years, there was no significant association between pantoprazole clearance and age or weight. AUC and C_{max} were in accordance with the data obtained from adults. 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.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard to 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 fore stomach 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 (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 fetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet Core
Sodium carbonate anhydrous
Mannitol
Crospovidone
Sodium lauryl sulphate
Polyvinyl pyrrolidone K90
Calcium stearate

Intermediate film coating: Opadry II HP 85F22138 yellow
Polyvinyl alcohol
Titanium dioxide

Macrogol/PEG 3350
Talc
Yellow iron oxide

Enteric film coating:
Acryl Eze Yellow (93092052)
Methacrylic acid and ethyl acrylate copolymer
Talc
Titanium dioxide
Triethyl citrate
Colloidal anhydrous silica
Sodium bicarbonate
Yellow iron oxide
Sodium lauryl sulfate
Simethicone Q7-2587

6.2 Incompatibilities
No known incompatibility.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 30°C.

6.5 Nature and contents of packaging
Aluminum/aluminum blister
In packs of 14 or 28 enteric coated tablets.

6.6. Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TURKEY
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8. MARKETING AUTHORIZATION NUMBER(S)
05584/07292/REN/2020

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of latest renewal: Dec 25, 2020

10. DATE OF REVISION OF THE TEXT

December 2018