SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANDEV 40 mg Enteric Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:	
Pantoprazole	40 mg (as sodium sesquihydrate)
Excipients:	
Sodium carbonate anhydrous	10 mg
Mannitol	89.25 mg
Sodium lauryl sulphate	1.65 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated tablets.
Light yellow, oblong enteric coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children over 12 years of age and adults:
It is indicated in the treatment of gastro-esophageal reflux disease.

Adults:
It is indicated in:
- Eradication of *Helicobacter pylori (H. pylori)* in combination with two appropriate antibiotics in duodenal and gastric ulcer associated with this organism.
- Treatment of peptic ulcer (duodenal ulcer and gastric ulcer),
- Treatment of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Children over 12 years of age and adults:
Gastro-esophageal reflux disease:
The recommended dose is 1 tablet of PANDEV 40 mg per day. In individual cases, the dose may be doubled (2 tablets of PANDEV 40 mg daily). For those patients who have not recovered after 4 weeks of treatment, an additional 4-week course may be considered.

Adults:
Eradication of *H. pylori* in combination with two appropriate antibiotic:
In *H. pylori* positive patients with gastric and duodenal ulcers, a combination therapy should be instituted for the eradication of the germ. For the resistance and appropriate prescribing, official regional guidelines such as national recommendations should be taken into account. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

a) Twice daily 1 tablet of PANDEV 40 mg Enteric Coated Tablets
- Twice daily 1000 mg amoxicillin
- Twice daily 500 mg clarithromycin

b) Twice daily 1 tablet of PANDEV 40 mg Enteric Coated Tablets
- Twice daily 400 – 500 mg metronidazole (or 500 mg tinidazole)
- Twice daily 250 – 500 mg clarithromycin

c) Twice daily 1 tablet of PANDEV 40 mg Enteric Coated Tablets
- Twice daily 1000 mg amoxicillin
- Twice daily 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second PANDEV 40 mg enteric coated 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 2 weeks. If pantoprazole therapy is to be continued for ulcer treatment, 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 PANDEV 40 mg enteric coated tablet monotherapy:

Treatment of gastric ulcer
1 tablet of PANDEV 40 mg is administered per day. In individual cases, the dose may be doubled (2 tablets of PANDEV 40 mg 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
1 tablet of PANDEV 40 mg is administered per day. In individual cases, the dose may be doubled (2 tablets of PANDEV 40 mg 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.

Long-term treatment of Zollinger-Ellison syndrome and other pathological hypersecretory conditions
Treatment should be started with a daily dose of 80 mg (2 tablets of PANDEV 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.

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

If drug product has been forgotten to take, the missed dose should not be taken. Treatment should be continued with the next dose according to patient's regular dosing schedule.

The doctor should be consulted regarding interruption or prematurely discontinuation of the treatment with PANDEV.

Additional information on special populations

Renal impairment

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

Hepatic impairment

A daily dose of 20 mg pantoprazole (1 tablet of PANDEV 20 mg) should not be exceeded in patients with severe liver impairment. PANDEV must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients. In addition, the liver enzymes should be monitored during the treatment, particularly for the long-term use, in these patients. In the case of a rise in the liver enzymes, the treatment with PANDEV should be discontinued.

Pediatric Population

PANDEV 40 mg is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in this age group (20 mg pantoprazole should be preferred for children aged 5-12 years).

Geriatric Population

No dose adjustment is necessary in the elderly.

4.3 Contraindications

PANDEV is contraindicated in patients who are hypersensitive to its active substance, substituted benzimidazoles, any of the excipients in its composition, or to other drugs used in combination.

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.

Combination therapy

In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be considered.

Presence of alarm symptoms

In the presence of any alarm symptom (e.g. unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anemia or melena) and when gastric ulcer is suspected or present, the possibility of malignancy should be excluded. Because pantoprazole can suppress symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with atazanavir

Co-administration of proton pump inhibitors is not recommended with atazanavir (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is mandatory, it is recommended to increase the dose of atazanavir to 400 mg and add 100 mg of ritonavir to the treatment, with careful clinical monitoring of the patient (e.g. viral load). A daily dose of 20 mg pantoprazole should not be exceeded.

Influence on vitamin B12 absorption
In conditions of pathologic hypersecretion that requires long-term therapy or in Zollinger-Ellison syndrome, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) caused by hypochlorhydria or achlorhydria. This should be considered in patients with reduced body reserves of vitamin B12 or at risk for vitamin B12 malabsorption 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.

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.

Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, and in most cases after a year of therapy. Serious manifestations of hypomagnesemia such as tetany, arrhythmia and convulsions can occur. In most patients, treatment of hypomagnesemia 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 hypomagnesemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Interactions with investigations for neuroendocrine tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop PPI treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Co-administration with non-steroidal anti-inflammatory drugs (NSAIDs)
The use of PANDEV for prevention of gastroduodenal ulcers induced by non-selective 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 (over 65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Gastrointestinal infections caused by bacteria

Like all proton pump inhibitors, pantoprazole might be expected to increase the number of bacteria normally present in the upper gastrointestinal tract. Treatment with PANDEV may lead to slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* (see section 5.1).

This medicinal product contains less than 10 g mannitol (89.25 mg) in each tablet, therefore, it is not considered to have a laxative effect.

This medicinal product contains less than 1 mmol (23 mg) sodium in each dose, therefore, it is considered 'sodium free' and no sodium-related adverse effect is expected.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on absorption of other drugs

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

HIV medications (atazanavir)

Co-administration of proton pump inhibitors 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. Therefore, co-administration of proton pump inhibitors, including pantoprazole, with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon and warfarin)

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

Other interaction studies

Pantoprazole is metabolized primarily 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 conducted with drugs that are metabolized via the same enzyme system including carbamazepine, diazepam, glibenclamide, nifedipine, and oral contraceptives containing levonorgestrel and ethinyl estradiol do not imply a clinically significant interaction.

A range of interaction studies demonstrate that pantoprazole does not interfere with either 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 p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed on concomitant administration of pantoprazole with antibiotics such as clarithromycin, metronidazole, and amoxicillin. No clinically relevant interaction has been found.

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

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is B.

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

Pregnancy
There is limited clinical experience with the use of pantoprazole during pregnancy.
Animal studies have shown reproductive toxicity (see section 5.3).
The potential risk for humans is unknown. PANDEV should not be used in pregnant women unless clearly necessary.
In animal reproduction studies, mild signs of fetotoxicity were observed at doses above 5 mg/kg. Caution should be exercised when used in pregnancy.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, a decision on whether to discontinue breast-feeding or to discontinue PANDEV therapy should take into account the benefit of breast-feeding for the child, and the benefit of PANDEV therapy for the woman.
Pantoprazole should be used in nursing mothers only if the benefit to the mother outweighs the potential risk to the infant.

Fertility
There was no evidence of impaired fertility or teratogenic effect in humans.
In animal reproduction studies, mild signs of fetotoxicity were observed at doses above 5 mg/kg. There is no evidence of infertility or teratogenicity (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). In the event of such adverse effects, 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 follows:
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).

Frequency Organ System	Common (≥1/100 <1/10)	Uncommon (≥1/1,000 <1/100)	Rare (≥1/10,000 <1/1,000)	Very rare (<1/10,000, including isolated reports)	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, Hypomagnesemia (see section 4.4)
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		
Ophthalmic disorders			Disturbances in vision (blurred vision)		
Gastrointestinal disorders		Nausea / vomiting, Abdominal pain and discomfort, Constipation, Dry mouth, Abdominal distension and bloating, Diarrhea			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury, Jaundice, Hepatocellular failure
Skin and subcutaneous tissue disorders		Allergic reactions such as: Itching, exanthema and rash; Pruritus	Urticaria, Angioedema		Stevens-Johnson syndrome, Lyell syndrome, Erythema multiforme, Photosensitivity
Musculoskeletal,		Fractures of the wrist, hip and	Arthralgia, Myalgia		

connective tissue disorders		spine (see section 4.4)			
Renal and urinary tract disorders					Interstitial nephritis
Reproductive system and breast disorders			Gynecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased, Edema peripheral		

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 in accordance with local requirements.

4.9 Overdose
There are no known symptoms of overdose in humans.
IV doses of up to 240 mg over 2 minutes have been administered and are 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 that inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps in the 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, and 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.

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 *Clostridium difficile* in hospital patients.

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

5.2 Pharmacokinetic properties

General specifications

Absorption

Pantoprazole is rapidly absorbed and the maximum plasma level is achieved even after a single 40 mg oral dose. Serum concentrations of approximately 2-3 mcg/mL are reached approximately 2.5 hours after administration, 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 Area Under the Curve (AUC), maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

Pantoprazole 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 that include oxidation by CYP3A4. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate.

Elimination

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest is excreted with the feces. The terminal half-life is about 1 hour and the clearance is about 0.11/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). 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 intravenous and oral administration.

Characteristics in patients

Polymorphic metabolism

Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolizers. 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 metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). 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 (including dialysis patients). 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 hours), 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 hours 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.

Pediatric 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 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 volume of distribution were in accordance with data from adults.

Geriatric population

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

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 tumors was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

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

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the fetus is increased shortly before birth

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Sodium carbonate anhydrous
Mannitol
Crospovidone
Sodium lauryl sulphate
Polyvinylpyrrolidone 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:
Talc
Titanium dioxide
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 25°C.

6.5 Nature and contents of packaging

Alu/Alu blister.
Each cardboard box contains 14 or 28 enteric coated tablets.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local disposal requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

209/79

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 24.11.2006
Date of latest renewal : 24.11.2011

10. DATE OF REVISION OF THE TEXT