

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole Teva 40 mg gastro-resistant tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient:

Each Pantoprazole Teva 40 mg gastro-resistant tablet contains 36 mg sorbitol.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

A light brownish yellow, oval, slightly biconvex tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

*Adults and adolescents 12 years of age and above*

- Reflux oesophagitis

*Adults*

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

### 4.2 Posology and method of administration

Pantoprazole Teva 40 mg tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with water.

#### Recommended dose

*Adults and adolescents 12 years of age and above*

#### Reflux oesophagitis

One tablet of Pantoprazole Teva per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole Teva daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

*Adults*

#### Eradication of *H. pylori* in combination with two appropriate antibiotics

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

- a) twice daily one tablet Pantoprazole Teva  
+ twice daily 1000 mg amoxicillin  
+ twice daily 500 mg clarithromycin
- b) twice daily one tablet Pantoprazole Teva  
+ twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)  
+ twice daily 250 - 500 mg clarithromycin
- c) twice daily one tablet Pantoprazole Teva  
+ twice daily 1000 mg amoxicillin  
+ twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second Pantoprazole Teva tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *H. pylori*, the following dose guidelines apply for Pantoprazole Teva monotherapy:

#### Treatment of gastric ulcer

One tablet of Pantoprazole Teva per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole Teva daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

#### Treatment of duodenal ulcer

One tablet of Pantoprazole Teva per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole Teva daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

#### Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 tablets of Pantoprazole Teva 40 mg). Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

#### Special populations

##### *Children below 12 years of age*

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

##### *Hepatic Impairment*

A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole Teva 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 Teva in combination treatment of these patients (see section 4.4).

*Renal Impairment*

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

Elderly

No dose adjustment is necessary in elderly patients.

**4.3 Contraindications**

Hypersensitivity to pantoprazole, substituted benzimidazoles, or to any of the excipients or of the combination partners.

**4.4 Special warnings and precautions for use***Hepatic Impairment*

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

*Combination therapy*

In combination therapy, the Summaries of Product Characteristics of the respective medicinal products should be observed.

*In the presence of alarm symptoms*

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or malaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

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

*Co-administered with atazanavir*

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

*Influence on vitamin B12 adsorption*

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment, 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*

Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

*Hypomagnesaemia*

Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause

hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

#### *Fractures of the hip, wrist and spine*

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in 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.

#### *Sorbitol*

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

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

#### *Effect of pantoprazole on the absorption of other medicinal products*

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicines as erlotinib.

#### *HIV medications (atazanavir)*

Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

#### *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.

#### *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 drugs 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.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

## **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. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

#### Lactation

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

#### 4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

#### 4.8 Undesirable effects

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common ( $\geq 1/10$ ); 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).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

Frequency	Uncommon	Rare	Very rare	Not known
<b>Organ system</b>				
<b>Blood and the lymphatic system</b>			Leucopenia, thrombocytopenia	
<b>Immune system disorders</b>		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
<b>Metabolism and nutrition disorders</b>		Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia ( <i>see section 4.4</i> )
<b>Psychiatric disorders</b>	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)
<b>Nervous system disorders</b>	Headache; Dizziness			
<b>Eye disorders</b>		Disturbances in vision / blurred		

		vision		
<b>Gastrointestinal disorders</b>	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
<b>Hepatobiliary disorders</b>	Liver enzymes increased (transaminases, $\gamma$ -GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
<b>Skin and sub-cutaneous tissue disorders</b>	Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
<b>Musculoskeletal, connective tissue disorders</b>	Fracture of the hip, wrist or spine (see section 4.4)		Arthralgia; Myalgia	
<b>Renal and urinary disorders</b>				Interstitial nephritis
<b>Reproductive system and breast disorders</b>		Gynaecomastia		
<b>General disorders and administration site conditions</b>	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

## 4.9 Overdose

There are no known symptoms of over dosage in man.

Systemic exposures 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 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 in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment of the parietal cells where it inhibits the H<sup>+</sup>, K<sup>+</sup>-

ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H<sub>2</sub> receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is administered orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. 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.

## 5.2 Pharmacokinetic properties

### Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average, the maximum serum concentrations are 2-3 µg/ml after 2.5 hours post-administration and these values remain constant after multiple administration.

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

### Distribution

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

### Elimination

The substance 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. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

### *Characteristics in patients/special groups of subjects*

Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

No dose reduction is requested when pantoprazole is administered to patients with restricted renal function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. 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 accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

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

#### *Children*

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5–16 years 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**

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year rodent studies an increased number of liver 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 foetus is increased shortly before birth.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### The core of tablet:

Mannitol  
Crospovidone (type B)  
Sodium carbonate, anhydrous  
Sorbitol (E420)  
Calcium stearate

#### The film-coating:

Hypromellose  
Povidone (K25)  
Titanium dioxide (E171)  
Iron oxide, yellow (E172)  
Propylene glycol  
Methacrylic acid - ethyl acrylate copolymer  
Sodium lauryl sulphate  
Polysorbate 80

Macrogol 6000  
Talc

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

5 years.

### HDPE tablet container:

Shelf life after the first opening is 3 months.

## **6.4 Special precautions for storage**

Blister pack: Store in the original package in order to protect from moisture.

Container: Keep the container tightly closed in order to protect from moisture.

## **6.5 Nature and contents of container**

Blister pack (OPA/Aluminium/PVC film and aluminium foil) in a carton box.

Pack-sizes of 7, 14, 15, 28, 30, 56, 60, 84, 98, 100, 100 x 1, 112 or 140 gastro-resistant tablets.

HDPE containers with a silica gel desiccant in a tamper evident PP screw-cap.

Pack-size of 100 and 250 gastro-resistant tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

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

## **7 MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Computerweg 10  
3542 DR Utrecht  
The Netherlands

## **8 MARKETING AUTHORISATION NUMBER**

PA 749/89/2

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

Date of first authorisation: 13th February 2009

Date of last renewal: 3rd March 2012

## **10 DATE OF REVISION OF THE TEXT**

September 2012