Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole Teva 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40mg pantoprazole as pantoprazole sodium sesquihydrate.
Excipients: contains sorbitol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant Tablets

Product imported from the Netherlands:
A light brownish-yellow Oval, slightly biconvex tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For relieving the symptoms and for short-term treatment of gastrointestinal diseases which require a reduction in acid secretion:
- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis
- Zollinger-Ellison syndrome and other hypersecretory conditions.

4.2 Posology and method of administration

Method of administration
Pantoprazole Teva 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

Duodenal ulcer
The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole Teva 40 mg gastro-resistant tablet). Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

Gastric ulcer and moderate and severe reflux oesophagitis
The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole Teva 40 mg gastro-resistant tablet). A four-week period is usually required for the treatment of gastric ulcers and reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Zollinger-Ellison-Syndrome and other hypersecretory conditions
In the treatment of Zollinger-Ellison syndrome and other hypersecretory conditions, the initial dose is 80 mg daily (2 Pantoprazole Teva 40 mg gastro-resistant tablets). Thereafter, the dosage can be increased or decreased 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 dosage 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.

Elderly
A daily dose of 40mg pantoprazole should not be exceeded.

Patients with hepatic impairment
Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (see section 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with pantoprazole should be discontinued.

Children
Pantoprazole Teva 40 mg gastro-resistant tablets should not be used in children.

4.3 Contraindications

Hypersensitivity to pantoprazole or to any of the excipients.

4.4 Special warnings and precautions for use

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; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

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).

Pantoprazole 40 mg is not intended for the treatment of mild gastrointestinal complaints, such as nervous dyspepsia.

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

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

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.

Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

There is no experience with the use of pantoprazole in children below 12 years of age.

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

Pantoprazole may markedly reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore co-administration of atazanavir with proton pump inhibitors including pantoprazole, is not recommended (see Section 4.4).

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. Interactions of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed with a number of such medicinal products or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

Even though no interactions with pantoprazole and phenprocoumon or warfarin have been observed in clinical pharmacokinetics studies, a few isolated post-marketing cases of INR value changes in concomitant treatment with these substances have been reported. If the patient is using coumarin-type anticoagulants, measurements of prothrombin time / INR values are recommended after the initiation and discontinuation of pantoprazole and in irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

4.6 Fertility, pregnancy and lactation

Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus or baby.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

Common ≥ 1/100 to < 1/10

Uncommon ≥ 1/1000 to ≤ 1/100

Rare ≥ 1/10 000 to ≤ 1/1000

Very rare < 1/10 000, including isolated reports

Frequency	Common	Uncommon	Rare	Very rare
Organ system				
Blood and the lymphatic system				Leucopenia, thrombocytopenia
Immune system disorders				Anaphylactic reactions including anaphylactic shock
Psychiatric disorders			Depression, hallucination, disorientation and confusion especially in pre-disposed	

			patients as well as the aggravation of these symptoms in case of pre-existence.	
Nervous system disorders	Headache	Dizziness, disturbances in vision (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, constipation, flatulence	Nausea, vomiting,	Dry mouth	
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Skin and sub-cutaneous tissue disorders		Allergic reactions such as pruritus and skin rash		Urticaria, angioedema, severe skin reactions such as Stevens Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy
Investigations				Increased liver enzymes (transaminases, γ-glutamyltransferase), elevated triglycerides, increased body temperature

4.9 Overdose

There are no known symptoms of over dosage in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable.

Cases of overdosage or poisoning should be treated according to the standard treatment practice of toxic conditions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02BC02

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 channel of the parietal cells where it inhibits the H^+, K^+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H_2 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, the substance can affect 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

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 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. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

Terminal half-life is about 1 h. 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).

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.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. 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.

Bioavailability
Pantoprazole is completely absorbed after oral 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.

Characteristics in patients/special groups of subjects
No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2−3 h), excretion is still rapid and thus accumulation does not occur. However, the daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function.

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

A slight increase in AUC and Cmax 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

Acute toxicity
In acute toxicity studies in mice, the LD_{50} values were found to be 370 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.
In the rat, the corresponding values were around 240 mg/kg for i.v. administration and 900 mg/kg for oral administration.

Chronic toxicity
Hypergastrinaemia and morphologic changes of the mucosa were observed in studies investigating repeated administration for up to 12 months in the rat and dog. Most of the effects were reversible and attributable solely to the drug action, i.e. suppression of acid secretion.

In long-term studies in the rat and dog, there was an increase in stomach and liver weights; the increase being reversible after the substance was discontinued. The increase in liver weight following highly toxic doses was seen as a result of the induction of drug-metabolising enzymes.

Thyroid activation in two rat experiments is due to the rapid metabolism of thyroid hormones in the liver and has also been described in a similar form for other drugs. Changes in the thyroid and associated reduced degradation of cholesterol have been observed in one-year studies in the rat and dog. Hypertrophy of the thyroid and increases in cholesterol levels are reversible.

In studies in the dog, a species-species specific pulmonary oedema was observed. The animal-specific metabolite, which was responsible for the oedema, could not be identified in man.

Carcinogenicity
In a 2-year carcinogenicity study in rats - which corresponds to lifetime treatment for rats - ECL cell carcinoids were found. 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 treatment. In addition, rats have more ECL cells in the mucosa of the glandular stomach than man, so that a larger number of responder cells for the increased gastrin values can become active.

ECL cell neoplasms were not observed in either the study in mice (24 months) or in long-term studies in the dog. In clinical studies (40−80 mg for 1 year), ECL cell density slightly increased.

In the two-year studies, an increased number of neoplastic changes of the liver was observed in rats and female mice and was interpreted as being due to pantoprazole's high rate of metabolism in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. In man, no changes in the thyroid hormones T3, T4 and TSH were observed. This high dose phenomenon in the rat is therefore not relevant for man.

Mutagenicity
In mutagenicity studies, there were no indications of a mutagenic action *in vivo* or *in vitro.*

Reproduction toxicology
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, the concentration of pantoprazole in the foetus is increased shortly before birth, regardless of the route of administration.

In humans, there is no experience of the use of the drug during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For Tablets sourced in the Netherlands:

The core of tablet:
mannitol
crospovidone (type B)
sodium carbonate, anhydrous
sorbitol (e420)
calcium stearate

The film-coating
hypromellose
povidone (K25)
titanium dioxide (E 171)
iron oxide, yellow (E172)
propylene glycol
methacrylic acid-ethylacrylate-copolymer
sodium lauryl sulfate
polysorbate 80
macrogol 6000
talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister packs of 30 tablets contained in an over labelled outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

WPR Healthcare Ltd
Unit 10
Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA565/34/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2011

10 DATE OF REVISION OF THE TEXT