Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole Teva 40 mg Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: 42.4 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for Solution for Injection or Infusion.

A white to almost white dry powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gastric and Duodenal ulcer
Reflux oesophagitis
Zollinger-Ellison Syndrome and other pathological hypersecretory conditions

4.2 Posology and method of administration

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

Intravenous administration of Pantoprazole 40 mg is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. Therefore, as soon as oral therapy is possible, treatment with Pantoprazole i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Recommended Dose
Gastric and Duodenal ulcer, reflux oesophagitis
The recommended intravenous dose is one vial (40 mg pantoprazole) of Pantoprazole 40 mg per day.

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 Pantoprazole. Thereafter, the dosage 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 dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg Pantoprazole is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special Populations
Paediatric patients
The experience in children is limited. Therefore, Pantoprazole 40 mg Powder for Solution for Injection or Infusion is not recommended for use in patients below 18 years of age until further data become available.

Hepatic impairment
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).

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

Elderly
No dose adjustment is necessary in elderly patients.

Method of administration
A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. For instructions for preparation see section 6.6. The prepared solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 55 mg/ml (5%) solution for injection.

After preparation, the solution must be used within 6 hours if it is stored at 25°C or within 24 hours at 2-8 °C.

The medicinal product should be administered intravenously over 2-15 minutes.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the other excipients.

4.4 Special warnings and precautions for use

In presence of alarm symptoms
In the presence of any alarm symptom (e. g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or 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.

Hepatic Impairment
In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued (see section 4.2).

Risk of fractures of 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.

Co-administration 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 (e.g virus load) 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.

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.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

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 such as ketoconazole, itraconazole, posaconazole and other medicine such 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 INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants, 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 (see section 5.3). 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 breast-feeding 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 (≥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).
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 Organ System	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1000, <1/100)**	**Rare ≥1/10,000, <1/1000)**	**Very rare (≤1/10,000, incl. Isolated reports)**	**Not Known**
Blood and lymphatic system				Leukopenia: Thrombocytopenia	
Immune system disorders			Hypersensitivity (Including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); weight changes		Hyponatraemia, Hypomagnesemaeia
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 case of pre-existence)

Nervous system disorders		Headache Dizziness;			
Eye Disorders			Disturbances in vision (blurred vision)		
Gastrointestinal disorders		Diarrhoea; Nausea / Vomiting; Abdominal distension and bloating; Constipation; Dry Mouth; Abdominal pain and discomfort			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; jaundice; Hepatocellular failure.
Skin and sub-cutaneous tissue disorders		Rash / Exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson Syndrome; Erythema Multi-forme; Lyell-Syndrome; Photosensitivity
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Athralgia; Myalgia		
Renal and urinary disorders					Interstitial nephritis
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

4.9 Overdose

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of 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 blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in 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 within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases 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 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.

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
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.

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

Elimination
The substance is almost exclusively metabolised 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 are excreted in the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolites (about 1.5 hours) is not much longer than that of pantoprazole.

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 required when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), excretion is still rapid and thus accumulation does not occur.
Although for patients with hepatic cirrhosis (classes A and B according to Child) the half-time values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum plasma 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 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 and weight. AUC and volume of distribution were in accordance with data from adults.

5.3 Preclinical safety data

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

In the two-year carcinogenicity study 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 tumours were 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 side 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

Disodium edetate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened Product: 24 months.

Product after reconstitution / dilution:
Chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and for 24 hours at 2-8°C. From microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstitued / diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

15 ml Type I clear glass vials closed with bromobutyl rubber stoppers and sealed with aluminium caps fitted with plastic flip-off discs. Pack sizes: 1, 5 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9mg/ml (0.9%) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a clear colourless or slightly brownish solution.

This solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 55 mg/ml (5 %) solution for injection.

After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 6 hours at 25 °C and for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately.

Pantoprazole should not be prepared or mixed with solvents other than those stated.
The medicine should be administered intravenously over 2-15 minutes.

The contents of the vial are for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 749/87/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th December 2010

10 DATE OF REVISION OF THE TEXT

August 2013