

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole Nycomed i.v. 40 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate)

Excipients:

Each vial contains 1mg disodium edetate and 0.24mg sodium hydroxide.

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection

A white to off-white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Reflux oesophagitis
- Gastric and duodenal ulcer
- 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 Nycomed is recommended only if oral application 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 Nycomed i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Recommended dosage

Gastric and duodenal ulcer, reflux oesophagitis

The recommended intravenous dose is one vial of Pantoprazole Nycomed (40 mg pantoprazole) 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 Nycomed. 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 dose 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 Nycomed 40 mg powder for solution for injection 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 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 12 hours.

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 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).

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*.

Sodium

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

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.

Bone fractures

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.

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 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 medicines 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 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 interaction studies

Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with 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 by concomitantly administering pantoprazole 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 5.3). The potential risk for humans is unknown. Pantoprazole Nycomed 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 Nycomed should be made taking into account the benefit of breast-feeding to the child, and the benefit of Pantoprazole Nycomed therapy to the woman.

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 ADR is injection site thrombophlebitis. Diarrhoea and headache occurred 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	Common	Uncommon	Rare	Very rare	Not known
System Organ Class					
Blood and lymphatic system			<u>Agranulocytosis</u>	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia (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 case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		
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-		Rash /	Urticaria;		Stevens-Johnson

cutaneous tissue disorders		exanthema / eruption; Pruritus	Angioedema		syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		
Renal and urinary disorders					Interstitial nephritis
Reproductive system and breast disorders			Gyaecomastia		
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 recommendation 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 does 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 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 includes 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 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.

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 kidney 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 – 3h), 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-lifetime 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 intravenous 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 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 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

disodium edetate

sodium hydroxide (for pH adjustment)

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: 2 years

After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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 reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

The powder for solution for injection is contained in a 10 ml clear glass vial (type I Ph. Eur) with aluminum cap and bromobutyl rubber stopper.

Pack sizes of 1 vial, 5 (5x1) vials

Hospital packs: 1, 5 (5x1), 10 (10x1) and 20 (20x1) vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the powder. The appearance of the product after reconstitution is a clear yellowish solution. This solution may be administered directly or may be administered after mixing with 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 55 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution.

After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25°C. From a microbiological point of view, the product should be used immediately. Pantoprazole Nycomed 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

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8 MARKETING AUTHORISATION NUMBER

PA1421/3/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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