Package Insert

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole-AFT 40 mg powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate).

For the full list of excipients, see 6.1 List of excipients

3 PHARMCEUTICAL FORM

Powder for solution for injection.

White to off-white porous cake or powder.

After reconstitution: Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short term use for symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate.

Therapeutic Indication	**Posology and method of IV administration**
Duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis	The recommended intravenous dosage is one vial (40 mg pantoprazole) Pantoprazole-AFT per day. As soon as oral therapy is possible, treatment with Pantoprazole-AFT should be discontinued and 40 mg pantoprazole p. o. should be administered instead. This medicine should be administered by a healthcare professional and under appropriate medical supervision. Intravenous administration of pantoprazole is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. *Method of administration* Pantoprazole should be administered intravenously after reconstitution, or

	reconstitution and dilution. A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution for injection. The prepared solution may be administered directly or may be administered after mixing it with 100 ml physiological sodium chloride solution for injection or 5% Glucose solution for injection. The resulting solution should be used within 12 hours and is for SINGLE USE ONLY. The medicinal product should be administered intravenously over 2 - 15 minutes. <u>*General instructions*</u> Keep the vial in the outer carton in order to protect from light. As soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued and 40 mg pantoprazole p. o. (by mouth) should be administered instead.

Special patient population

Paediatric patients

The experience in children is limited. Pantoprazole-AFT powder for solution for injection is not recommended for use in patients below 18 years of age.

Impaired hepatic function

A daily dose of pantoprazole 20 mg should not be exceeded in patients with severe liver impairment (See section 4.4).

Impaired renal function

No dose adjustment is necessary in those with impaired renal function.

Elderly patients

Generally, no dose adjustment is necessary in elderly patients. However, the daily dose of 40 mg should not be exceeded in treatment of gastric or duodenal ulcer.

4.3 CONTRAINDICATIONS

Pantoprazole-AFT should not be used in cases of known hypersensitivity to any of the constituents.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate.

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 daily dose has to be reduced to 20mg pantoprazole. In patients with severe liver impairment, liver enzymes should be monitored during therapy regularly. In the case of a rise of the liver enzymes, the treatment should be discontinued. (See Dosage and Method of Administration).

Gastrointestinal infections caused by bacteria, including *Clostridium difficile*

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-AFT may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*. In hospitalized patients, PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Published observational studies suggest that proton pump inhibitor (PPI) therapy like pantoprazole may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see 4.8 Undesirable Effects). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Pantoprazole-AFT, refer to Warnings and Precautions sections of those package inserts.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious manifestations of hypomagnesamia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmias can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. [See Undesirable effects].

Bone Fractures

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 daily 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. Patients at risk for osteoporosis- related fractures should be managed according to established treatment guidelines (see Dosage and Administration and Undesirable effects).

Concomitant use with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients (see Drug Interactions).

HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Influence on vitamin B12 absorption

Daily treatment with any acid-suppressing medication over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long- term therapy or if relevant clinical symptoms are observed.

Interference with Laboratory Tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE)

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients

ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving pantoprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (See section 4.8). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs with pH-Dependent Absorption Pharmacokinetics:

Pantoprazole-AFT may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

HIV medications (e.g. atazanavir)

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

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 bioavailibility of atazanavir. The absorption of atazanavir is pH dependent.

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) and prothrombin have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients

treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of increase prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (see Warnings and Precautions).

Other interaction studies

Pantoprazole is 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.

An interaction 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 in interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin and an oral contraceptive containing levonorgestrel and ethinyl oestradiol.

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 also 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.

Clopidogrel

Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Drugs that Inhibit or Induce CYP2C19

Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole. Inducers of CYP2C19 may decrease the systemic exposure to pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy

The limited data from the use of pantoprazole in pregnant women does not indicate foetal/ neonatal toxicity. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pantoprazole-AFT should not be used during pregnancy, unless clearly necessary.

Use in 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-AFT should be made taking into account the benefit of breastfeeding to the child, and the benefit of Pantoprazole-AFT therapy to women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or 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 ADVERSE EFFECTS (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 below table lists adverse drug reactions reported with pantoprazole in clinical studies and post- marketing experience. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines:

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.

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

Organ class	Frequency				
	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**
Blood and lymphatic system			Agranulo-cytosis	Leukopenia; Thrombo-cytopenia; Pancytopenia	
Immune system disorders			Hyper-sensitivity (including anaphylactic reactions including anaphylactic shock)		Systemic lupus erythematosus
Metabolism and nutrition disorders			Hyper-lipidaemia; Weight changes		Hyponatraemia; Hypo-magnesaemia; Hypocalcemia*; Hypokalemia*
Psychiatric disorders		Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Nervous system disorders		Headache, Dizziness	Taste Disorders		
Eye disorders			Distur-bances in vision/ blurred vision		
Gastro-intestinal disorders		Diarrhoea Nausea; vomiting; Abdominal distension and bloating; Constipation; Dry mouth; abdominal pain and discomfort			
Hepato-biliary disorders		Liver enzymes increased	Bilirubin increased		Hepatocellular injury, jaundice, hepatocellular failure

Organ class	Frequency				
	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**
Skin and sub-cutaneous tissue disorders		Rash/ Exanthema; eruption; Pruritus	Urticaria Angioedema;		Stevens-Johnson syndrome; Toxic epidermal necrolysis; Erythema multiforme; Photosensitivity, Cutaneous lupus erythematosus; DRESS^; Acute generalized exanthematous pustulosis
Musculo-skeletal, connective tissue disorders			Arthralgia; Myalgia		Fracture of wrist, hip and spine
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)
Repro-ductive system and breast disorders			Gyneco-mastia		
General disorders and adminis-tration site conditions	Injection site thrombo-phlebitis	Asthenia; Fatigue and Malaise	Body temper-ature increased; Peripheral oedema		

* Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia (see Special Warnings and Special Precautions for use, 4.4)
^DRESS: Drug Rash with Eosinophilia and Systemic Symptoms

4.9 OVERDOSE

Systemic exposure with doses up to 240 mg administered intravenously over 2 minutes was well tolerated.

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

In the case of overdose with clinical signs of intoxication, the usual rules of intoxication therapy apply.

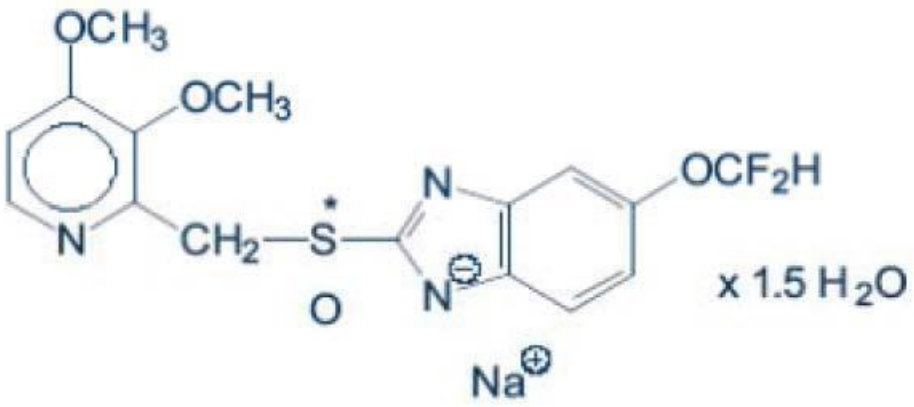
4.10 DRUG ABUSE AND DEPENDENCE

Drug dependence has not been observed.

5 PHARMACOLOGICAL PROPERTIES

Pantoprazole-AFT contains pantoprazole, a proton pump inhibitors which inhibits the gastric H^+K^+ ATPase which is responsible for acid secretion in the parietal cells of the stomach. Pantoprazole is white to off-white powder with a molecular weight of 432.4. Pantoprazole is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. Pantoprazole is a racemic mixture with a melting point of 138 °C.

The chemical name for pantoprazole is sodium-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2- pyridinyl)methyl] sulfinyl]-1 H-benzimidazole sesquihydrate and is represented by the following chemical structure :



Empirical chemical structure: $C_{16}H_{14}F_2N_3NaO_4S \times 1.5H_2O$

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic / indication group / action mechanism

Selective proton pump inhibitor, substituted benzimidazole

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 canaliculi 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 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 active substance is given 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 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 and liver enzymes according to results in animal studies.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics.

Distribution

Pantoprazole's serum protein binding is about 98%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

Metabolism

Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver. Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

Excretion and elimination

About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the feces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate.

$T_{1/2}$ of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

Special population

Impaired renal function

In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy 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.

Impaired hepatic function

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h (pantoprazole 20 mg tablet) and the AUC values increased by a factor of 3 – 5 (pantoprazole 20 mg tablet), the maximum serum concentration only increased slightly by a factor of 1.3 (after oral administration) compared with healthy subjects.

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

Age, Gender, Race

As with other clinically used PPIs, a small percentage of the population (about 3% Caucasians, 20% Asians) shows slower elimination of pantoprazole ($T_{1/2}$ being up to 10 hours as compared with 1 hour).

Such persons are known as poor metabolizers as a result of a deficiency of the CYP2C19 enzyme. 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.

Compared with younger subjects, slight increases in AUC and C_{max} were noted after single and repeated oral administration of pantoprazole to healthy elderly subjects (age >65 years). However, no dose adjustment is generally necessary in elderly patients.

Drug interactions

Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out.

Nevertheless, in specific tests pantoprazole did not affect the clearance of several compounds metabolized by CYP enzymes. Vice-versa, all drugs that were tested regarding their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.

No detectable interactions between pantoprazole and any other commonly prescribed co-medication tested so far were found.

Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol), or does not interfere with pglycoprotein 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.

(See Interaction with other medicinal products and other forms of interaction).

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Non-clinical 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 it can be concluded 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.

Animal Toxicology and/or Pharmacology

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 to the thyroid glands are expected.

In animal reproduction studies, signs of fetotoxicity were observed at doses above 3 mg/kg.

Investigations revealed no evidence of impaired fertility or teratogenic effects. Crossing 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 fetus is increased shortly before birth.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Tribasic sodium phosphate dodecahydrate

6.2 PRODUCT DESCRIPTION

Pantoprazole-AFT is a White to off-white porous cake or powder supplied in 10 mL sterile vial (type I). 10 vials are packed in a carton.

6.3 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section “Instructions for use/ handling”.

6.4 STORAGE CONDITIONS AND SHELF LIFE

Pantoprazole-AFT should be stored below 25 °C, protected from light. The expiry date of this pack is printed on the container. Do not use this pack after the expiry date.

The reconstituted and the diluted solution should be used within 12 hours when stored below 25 °C. However, to reduce microbiological hazard, use as soon as practicable after reconstitution/preparation.

6.5 INSTRUCTIONS FOR USE/ HANDLING

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This reconstituted solution may be administered directly or may be administered after mixing with 0.9% Sodium Chloride Intravenous Infusion or 5% Glucose Intravenous Infusion or Ringer’s Lactate injection.

For reconstitution and mixing, follow the below mentioned procedure:

Dissolve a vial of pantoprazole lyophilisate for solution for injection with 10 ml of 0.9% sodium chloride injection. Transfer 2 vials of reconstitution solution of pantoprazole lyophilisate for solution for injection to 80 ml of 0.9% sodium chloride injection, 5% glucose injection or Ringer’s lactate injection respectively, to obtain the diluted solution of a total volume of 100 ml and the concentration of 0.8 mg/ml.

This product contains no antimicrobial agent. Pantoprazole-AFT injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g., if cloudiness or precipitation is observed), should be discarded.

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

7 PRODUCT OWNER

AFT Pharmaceuticals Ltd.

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8 DATE OF REVISION

October 2023