

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole Bluefish 20 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

Yellow, oval, biconvex and smooth tablets.

The tablet dimensions are the following:

- Width: 5.85 mm $\pm$ 0.29 mm (5.56 mm – 6.14 mm)
- Length: 8.35 mm $\pm$ 0.42 mm (7.93 mm – 8.77 mm)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pantoprazole Bluefish is indicated for use in adults and adolescents 12 years of age and above for:

- Symptomatic gastro-oesophageal reflux disease.
- Long-term management and prevention of relapse in reflux oesophagitis.

Pantoprazole Bluefish is indicated for use in adults for:

- Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years of age and above

Symptomatic gastro-oesophageal reflux disease

The recommended oral dose is one Pantoprazole Bluefish 20 mg tablet per day. Symptom relief is generally accomplished within 2–4 weeks. If this is not sufficient, symptom relief

will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis

For long-term management, a maintenance dose of one Pantoprazole Bluefish 20 mg tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole Bluefish 40 mg gastro-resistant tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Adults

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dose is one Pantoprazole Bluefish 20 mg tablet per day.

Children below 12 years of age

Pantoprazole Bluefish is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in this age group (see section 5.2).

Patients with hepatic impairment

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

Patients with renal impairment

No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

Older people

No dose adjustment is necessary in older people (see section 5.2).

Method of administration

Oral use

Pantoprazole Bluefish 20 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with water one hour before a meal.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Hepatic Impairment

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

Co-administration with NSAIDs

The use of Pantoprazole Bluefish 20 mg as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Gastric malignancy

Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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.

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

Co-administration with 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, due to significant reduction in their bioavailability (see section 4.5).

Influence on vitamin B12 absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Long term treatment

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal infections caused by bacteria

Treatment with Pantoprazole Bluefish may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Pantoprazole Bluefish. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Pantoprazole Bluefish treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH-Dependent Absorption Pharmacokinetics

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral availability, e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

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 due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate

Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where

high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

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.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not affect 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.

Medicinal products that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John's wort (*Hypericum perforatum*) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or fetotoxicity of Pantoprazole Bluefish.

Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Pantoprazole Bluefish during pregnancy.

Breast-feeding:

Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision

on whether to discontinue breast-feeding or to discontinue/abstain from Pantoprazole Bluefish therapy should take into account the benefit of breast-feeding for the child, and the benefit of Pantoprazole Bluefish therapy for the women.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3)

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

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

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

Frequency	Common	Uncommon	Rare	Very rare	Not known
System Organ Class					
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides,		Hyponatraemia; Hypomagnesaemia (see section 4.4); Hypocalcaemia in

			cholesterol); Weight changes		association with hypomagnesaemia; Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	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 subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyellsyndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances

Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 an 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 in 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 administered orally or intravenously.

Pharmacodynamic effects

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 and liver enzymes according to results in animal studies.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1–1.5 µg/ml are achieved, and these values remain constant after multiple administration. Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

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

Distribution

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

Biotransformation

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.

Elimination

Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the

proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

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

Special populations

Poor metabolisers

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.

Renal impairment

No dose reduction is recommended 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 dialyzed. Although the main metabolite has a moderately delayed half-life (2–3h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment

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

Older people

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

Paediatric population

Following administration of single oral doses of 20 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

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

In a 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 two-year rodent studies an increased number of liver tumours was observed in rats (in one rat study only) 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) in one 2 year study. 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 phosphate anhydrous
Mannitol
Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate
Hypromellose
Triethyl citrate
Sodium starch glycolate (Type A)
Methacrylic acid-ethyl acrylate copolymer (1:1)
Yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu/Alu blister: 14, 28, 56, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed Nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed Nationally]

10. DATE OF REVISION OF THE TEXT

2018-07-27