SUMMARY OF PRODUCT CHARACTEISTICS

ANTOPRAZ (Pantoprazole for Injection 40 mg.)

English

1. Name of the medicinal product;

ANTOPRAZ (Pantoprazole for injection 40 mg.)

2. Qualitative and quantitative composition :

Each vial contains:
Pantoprazole sodium USP equivalent to Pantoprazole……40 mg

3. Pharmaceutical form

Lyophilized cake (for reconstitution)

Appearance: Almost white Lyophilized cake

4. Clinical particulars:

4.1 Therapeutic indications:

Antopraz is a preparation intended to treat disease of the stomach and intestine related to acidity. This is a "selective inhibitor of the proton pump" which decreases the amount of acid produced in your stomach.

Antopraz is used for the treatment of:

- Moderate to severe Gastroesophageal Reflux Disease (inflammation of the oesophagus due to reflux of stomach acid)

- Duodenal ulcer
- Stomach ulcer (gastic)
- The Zollinger-Ellison syndrome and other disorder including hypersecretary condition of stomach.

4.2 Posology and Method of administration:

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

The intravenous administration of pantoprazole 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 I.V. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis

The recommended intravenous dose is one vial 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 of pantoprazole I.V. 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 of pantoprazole I.V. is sufficient to manage a decrease of acid output into the target range (< 10 m Eq/h) within one hour in the majority of patients.

Special populations

Paediatric population: The experience in children is limited. Therefore, pantoprazole I.V. 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:

Dissolve the powder 40 mg into the vial of freeze-dried 10 ml solution of sodium chloride 0.9%
The resulting solution can be administered by direct injection or slow infusion
The administration will be carried out from 2 to 15 minutes.
This reconstituted solution may be diluted in 100 ml of saline or glucose solution 5%
After preparation, the solution must be used within 12 hours.

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:

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 in the liver enzymes, the treatment should be discontinued (seesection 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 (e.g. Salmonella and Campylobacter and C.difficile).

Sodium

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

4.5 Interaction with other medicinal and other forms of interactions:

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 dependant 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.

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 metabolised 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 metabolised 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 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.

Breastfeeding:
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).

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

Frequency	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
System organ class					
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-cytopenia-; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemia and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia; Hypocalcaemia in association with hypomagnesaemia; Hypokalaemia

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		Paraesthesia
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; Lyell syndrome; Erythema multiforme; Photo-sensitivity
Musculo-skeletal and connective tissue disorders			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	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 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 (similar 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 pathways include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were few cases of subjects with delayed elimination. Because of 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 metabolite (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 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 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 liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 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.

Paediatric population

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:

Not applicable

6. Pharmaceutical particulars;

6.1 List of excipients

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:

As packaged for sale: 2 years
Reconstituted solution should be used immediately

6.4 Special precautions for storage:

Store in cool and dry place, below 30° C, protected from light

6.5 Nature and contents of container:

USP glass vial type I, Amber glass vial, sealed with a grey chlorobutyl stopper and an aluminium flip-off cap, containing 40 mg pantoprazole for injection as lyophilized cake

6.6 Special precautions for disposal and other handling:

A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the lyophilised powder. The reconstituted solution should be clear and colourless. This solution may be administered directly or may be

administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution

Pantoprazole for Injection 40 mg should not be prepared or mixed with solvents other than those stated.

This medicine should be administered intravenously over 2- 15 minutes.

The content of the vial is 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:

BLISS GVS PHARMA LTD.
102, Hyde Park, Saki-Vihar Road, Andheri (East) Mumbai 400 072, India

8. Number(S) in the National Register of finished pharmaceutical products:

Not Applicable

9. Date of first authorisation/renewal of the authorisation:

Not Applicable

10. Date of revision of the text:

Not Applicable