1. **Name of the Medicinal Product**
   Panopaz Tablets
   (Pantoprazole sodium delayed-release tablets USP)

2. **Qualitative and Quantitative Composition**
   Qualitative Composition
   Each enteric coated tablet contains:
   Pantoprazole sodium USP
   Equivalent to Pantoprazole …….. 40 mg

Sr. No.	Ingredients	Standards
1	Pantoprazole sodium equivalent to Pantoprazole	USP
2	Microcrystalline cellulose	BP
3	Lactose	BP
4	Magnesium stearate	BP
5	Croscarmellose sodium	BP
6	Ethylcellulose	BP
7	Isopropyl alcohol	BP
8	Acrycoat L-100	IH
9	Acetone	BP
10	Purified talc	BP
11	Titanium dioxide	BP
12	Macrogol 6000	BP
13	Colour: Tartrazine	IH

Quantitative Composition
Each enteric coated tablet contains:
Pantoprazole sodium USP
Equivalent to Pantoprazole …….. 40 mg

Sr. No.	Ingredients	Standards	Quantity/Batch of 1,00,000 tablets
1	Pantoprazole sodium Equivalent to Pantoprazole	USP	4.000 Kg
2	Microcrystalline cellulose	BP	4.500 Kg
3	Lactose	BP	5.300 Kg
4	Magnesium stearate	BP	0.160 Kg
5	Croscarmellose sodium	BP	1.000 Kg
6	Ethylcellulose	BP	0.040 Kg
7	Isopropyl alcohol	BP	9.800 Kg
8	Acrycoat L-100	IH	0.498 Kg
9	Acetone	BP	3.832 Kg
10	Purified talc	BP	0.147 Kg
11	Titanium dioxide	BP	0.005 Kg
12	Macrogols 6000	BP	0.236 Kg
13	Colour: Tartrazine	IH	6.000 g

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3. Pharmaceutical Form
Enteric coated tablet

4. Clinical Particulars
4.1 Therapeutic indications
Adults and adolescents 12 years of age and above.
- Reflux oesophagitis

Adults
- Eradication of *Helicobacter pylori (H. pylori)* in combination with appropriate antibiotics therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcer.
- Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions.

4.2 Posology and method administration
Panopaz tablets should not be chewed or crushed, and should be swallowed whole one hour before a meal with some water.
Recommended dose:
Adults and adolescents 12 years of age and above:

Reflux oesophagitis
One pantoprazole 40 mg gastro-resistant tablet per day. In individual cases, the dose may be doubled (increase to two tablets daily) especially when there has been no response to other treatment. A four week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Adults
Eradication of *H.pylori* in combination with two appropriate antibiotic:
In *H.pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance patter, the following combinations can be recommended for the eradication of *H pylori*:
a) twice daily one Pantoprazole 4 mg gastro-resistant tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin
b) twice daily one pantoprazole 40 mg gastro-resistant tablet
+ twice daily 400-500 mg metronidazole (or 500 mg tinidazole)
+ twice daily 250-500 mg clarithromycin
c) twice daily one Pantoprazole 40 mg gastro-resistant tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 400-500 mg metronidazole (or 500 mg tinidazole)
In combination therapy for eradication of H. pylori infection. , the second pantoprazole 40 mg gastro-resistant tablet should be taken one hour before the evening meal. The combination therapy is implemented for seven days in general and can be prolonged for a further seven days to a total duration of

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up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.
If combination therapy is not an option e.g if the patient has tested negative for *H. pylori*, the following dose guidelines apply for pantoprazole monotherapy:

Treatment of gastric ulcer:
One pantoprazole 40 mg gastro-resistant tablet per day.
In individual cases, the dose may be doubled (increase to two tablets daily) especially when there has been no response to other treatment. A four week period is usually required for the treatment of gastric ulcers. If this is not sufficient , healing will usually be achieved within a further four weeks.

Treatment of duodenal ulcer
One pantoprazole 40 mg gastro-resistant tablet per day. In individual cases, the dose may be doubled (increase to two tablets daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within two weeks. If a two week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions
For the long-term management of Zolinger-Ellison-Syndrome and other pathological hypersecretory conditions, patients should start their treatment with a daily dose of 80 mg (two tablets of pantoprazole 40 mg).Thereafter, the dose 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.
Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Special populations
Children below 12 years of age:
Pantoprazole 40 mg gastro-resistant tablets are not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic Impairment
A daily dose of 20 mg pantoprazole (one tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole gastro-resistant tablets must not used in combination treatment for eradication of *H.pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole gastro-resistant tablets in combination treatment of these patients.

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Renal impairment
No dose adjustment is necessary in patients with impaired renal function. Pantoprazole gastro-resistant tablets must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of pantoprazole gastro-resistant tablets in combination treatment for those patients.

Elder
No dose adjustment is necessary in the elderly.

4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the other excipients or of the combination partners.

4.4 Special warning 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 in liver enzymes, the treatment should be discontinued.

Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

In the presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematenesis, 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.

Co-administration with atazanavir
Co-administration with atazanavir with proton pump inhibitors is not recommended. 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.
In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo or achiorhydria. 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 symptons are observed.

Long term treatment

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

Risk of fracture
Proton pump inhibitors, especially if used in high 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 recognized 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.

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhihbitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter.*

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPis with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics) health care professionals should consider measuring magnesium levels before staring PPI treatment and periodically during treatment.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of pantoprazole on the absorption of other medicinal products:
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other 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.

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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 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 ethinyloestradiol 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), CYP2Ee1 (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. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use machine
Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

4.8 Undesirable effects

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Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhea and headache, both occurring in approximately 1% of patients.
The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a not known frequency.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

System Organ Class	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Thromno-cytopenia: Leukopenia	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders		Hyperlipi-daemias and lipid increases (triglycerides, cholesterol); weight changes		Hyponatraemia hypomagnesaemia (see special warning and precautions for use (4.4)
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucinations; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.
Nervous system disorders	Headache; dizziness			

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System Organ Class	Uncommon	Rare	Very rare	Not known
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 (trans-aminases, γ-GT)	Bilirubin increased		Hepatocellular injury; jaundice; hepatocellular failure
Skin and subcutaneous tissue disorders	Rash/ exanthema/ eruption; Pruritus	Urticaria; Angioedema		Stevens-johnson syndrome; lyell syndrome; Erythema multiforme; Photo-sensitivity
Musculoskeletal and connective tissue disorders	Fracture of the hip, wrist or spine	Athralgia; Myalgia		
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Asthenia, fatigue and malaise	Body temperature increased; oedema peripheral		

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4.9 Overdose

There are no known symptoms of overdose in man.

Systemic exposure with up to 240 mg administered intravenously over two 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, 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 two 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 the stimulation by other substances (acetylcholine, histamine, gastrin).

Pantoprazole has the same effect whether administered 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 have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on enocrine parameters of the thyroid according to results in animal studies.

5.2 Pharmacokinetic properties

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Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2-3 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 concentrations 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.

Elimination

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is dementhylation 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 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.

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 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 metabolisers than in subjects having a functional CYP2C19 enzymes (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 (two to three 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 seven and nine hours and the AUC values increased slightly by a factor of five to seven 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 oral doses of 20 or 0 mg pantoprazole to children aged 5 to 16 years AUC and Cmax were in the range of corresponding values in adults.

Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 to 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 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 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 included 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 fetus is increased shortly before birth.

6. Pharmaceutical Particulars

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6.1 List of excipients
Microcrystalline cellulose BP
Lactose BP
Magnesium stearate BP
Croscarmellose sodium BP
Ethylcellulose BP
Isopropyl alcohol BP
Acrycoat L-100 IH
Acetone BP
Purified talc BP
Titanium dioxide BP
Macrogols 6000 BP
Colour: Tartrazine supra

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months from the date of manufacturing

6.4 Special precautions for storage
Store below 30°C, protected from light and moisture.

6.5 Nature and content of container
10 tablets are packed in an Alu-Alu strip. Such 1 strip is packed in a printed carton along with a pack insert. Such 10 cartons are packed in an outer carton.

6.6 Special precautions for disposal and other handling
No special requirements.

7. **Marketing Authorization Holder and Manufacturing Site Address**
   Aglowmed Limited
   Office:
   702-A, Poonam Chambers, Worli,
   Mumbai-400 018, India.
   Email: ibd@aglowmed.com

   Manufacturing Facility:
   50/51, Raipur, Bhagwanpur, Roorkee,
   Dist. Haridwar, Uttarakhand, 247 661

8. **Marketing Authorization Number**
   Not applicable

9. **Date of First Authorization/ Renewal of Authorization**
   Not applicable

10. **Date of Revision Text**
    Not applicable

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