1.6.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished Pharmaceutical Product

1.1 Product name:
PANTO-40
(Pantoprazole Sodium Delayed Release Tablets USP 40 mg)

1.2 Strength:
Each enteric coated tablet contains:

Pantoprazole Sodium Sesquihydrate	BP
Eq. to Pantoprazole	40 mg
Excipients	Q.S
Colour: Red Oxide of Iron	

1.3 Pharmaceutical dosage forms:
Oral-Enteric coated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Label Claim (mg)	Req. Qty/Tablet (mg)	Req. Qty/Batch (Kg)	Functions
Dry Mixing					
1.	Pantoprazole Sodium Sesquihydrate BP Eq to Pantoprazole*	40.000	45.120	4.512	Proton Pump Inhibitor
2.	Croscarmellose sodium BP**	-	8.000	0.800	Disintegrant
3.	Mannitol BP	-	68.380	6.838	Diluent
4.	Anhydrous Sodium carbonate BP	-	9.000	0.900	Alkalizing agent
Binding					
5.	Povidone K – 30 BP	-	3.500	0.350	Binder
6.	Isopropyl Alcohol BP***	-	0.05 ml	5.000 Ltr	Solvent
Lubrication					
7.	Calcium Stearate BP	-	4.000	0.400	Lubricant
8.	Purified Talc BP	-	4.000	0.400	Glidant
9.	Croscarmellose sodium BP	-	8.000	0.800	Disintegrant
Weight of Uncoated Tablets			**150.000 mg**	**15.000 Kg**	
Enteric Coating					
10.	Colorezy White 17K680000 IH	-	4.500	0.450	Seal Coat Material. Moisture Barier
11.	Methylene chloride BP***	-	0.0340 ml	3.400 Lit	Solvent
12.	Isopropyl alcohol BP***	-	0.0340 ml	3.400 Lit	Solvent

13.	Enteric coat red iron oxide IH	-	18.000	1.800	Colorant
14.	Methylene chloride BP***	-	0.1620 ml	16.200 Lit	Solvent
15.	Isopropyl alcohol BP***	-	0.090 ml	9.000 Lit	Solvent
Weight of Enteric Coated Tablets			**172.50 mg**	**17.25 kg**	

*Quantity to be calculated on the basis of its potency (100.00 %)

Calculation:

Pantoprazole Sodium Sesquihydrate BP Eq to Pantoprazole 40 mg

Calculation:

$$= \frac{\text{Label claim X Mol Wt of Pantoprazole Sodium Sesquihydrate}}{\text{Mol wt of Pantoprazole}}$$

$$= \frac{40 \times 432.4}{383.4}$$

= 45.12 mg

** Quantity to be compensates on increasing quantity of active material.
*** The materials that will not remain in the final product.

Composition of Colorezy white 17K680000 (Seal Coat):

Components	Specification
HPMC	BP
PEG 6000	BP
Triacetin	BP
Purified Talc	BP
Titanium Dioxide	BP

Composition of Enteric Coat Red oxide of Iron:

Components	Specification
Cellulose Acetate Phthalate	BP
Ethyl Cellulose	BP
Titanium Dioxide	BP
Purified Talc	BP
Diethyl phthalate	BP
Colour Lake of red iron oxide	IH

3. Pharmaceutical forms

Reddish brown coloured, round, biconvex, both side plain enteric coated tablet.

4. Clinical Particulars

4.1 Therapeutic Indications

Pantoprazole is a proton pump inhibitor indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)
- Maintenance of Healing of Erosive Esophagitis
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

4.2 Posology and Method of administration

Posology

Adults and adolescents 12 years of age and above

Reflux oesophagitis

One tablet of Pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults

Eradication of H. pylori in combination with two appropriate antibiotics

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 pattern, the following combinations can be recommended for the eradication of H. pylori:

a) Twice daily one tablet Pantoprazole
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) Twice daily one tablet Pantoprazole
+ twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)
+ twice daily 250 - 500 mg clarithromycin

c) Twice daily one tablet Pantoprazole
+ 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 tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of 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 tablet of Pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets of Pantoprazole daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Treatment of duodenal ulcer

One tablet of Pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets of Pantoprazole daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions patients should start their treatment with a daily dose of 80 mg (2 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 hyper secretory conditions is not limited and should be adapted according to clinical needs.

Patients with hepatic impairment

A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole must not be 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 in combination treatment of these patients.

Patients with renal impairment

No dose adjustment is necessary in patients with impaired renal function. Pantoprazole 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 in combination treatment for these patients.

Older people

No dose adjustment is necessary in older people.

4.3 Method of administration

For Oral use only
The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

4.4 Contraindications

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other constituents of the formulation.

4.5 Special warning and precaution 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.
Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.
Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom 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.
Influence on vitamin B12 absorption
In patients with Zollinger-Ellison syndrome and other pathological hyper secretory conditions requiring long-term treatment, 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 may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. 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 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 medicinal products that may cause hypomagnesaemia, 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 older people or in the 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.

Sub-acute 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 healthcare professional should consider stopping Pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

4.6 Paediatric population

Pantoprazole is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in the age group.

4.7 Interaction with other medicinal products and other forms of interactions

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 such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibtiors

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.

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 inhibitors 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 medicinal products 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.

4.8 Additional information on special populations

Not Available

4.9 Paediatric population

Pantoprazole is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in the age group.

4.10 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of Pantoprazole.
Animal studies have shown reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of Pantoprazole 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 therapy taking into account the benefit of breast-feeding for the child, and the benefit of Pantoprazole therapy for the woman.
Fertility
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies

4.11 Effects on ability to drive and use machines

Pantoprazole has no or negligible influence on the ability to drive and use machines.
Adverse drug reactions, such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

4.12 Undesirable effects

The most frequently occurring adverse reactions are as follows:

- For adult use (>2%) are headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.
- For pediatric use (>4%) are URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.

4.13 Overdose

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.
Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

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 endocrine parameters of the thyroid according to results in animal studies.

ATC code- A02BC02

5.2 Pharmacokinetic Properties

<u>Absorption</u>
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 does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.
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 - 3 h), 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 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

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 or 40 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 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 fore stomach 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 tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. Pharmaceutical Particulars

6.1 List of Excipients

Croscarmellose Sodium BP
Mannitol BP
Anhydrous Sodium carbonate BP
Povidone K – 30 BP
Isopropyl Alcohol BP
Calcium Stearate BP
Purified Talc BP
Colorezy White 17K680000 IH
Methylene chloride BP
Enteric coat Red iron oxide IH

6.2 Incompatibilities

None known.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30˚C in dry place, Protected from light. Keep out of reach of children.

6.5 Nature and contents of container

Packing: 1 X 10 Tablets in Alu-Alu Blister Pack

Primary Packing: 10 Tablets packed in Printed Aluminium foil from one side and Plain Aluminium foil from the other side.

Secondary Packing: Such 1 Blister is packed in printed carton along with package insert.

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder and manufacturing site addresses

STALLION LABORATORIES PVT.LTD.
817, 8TH FLOOR, DEVPATH, OFF C. G. ROAD,
B/H LAL BUNGLOW, NR. SUPERMALL,
AHMEDABAD –380 006,
GUJARAT, INDIA.

8. Marketing authorisation numbers

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9. Date of First Registration/Renewal of the Registration

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10. Date of revision of Text

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11. Dosimetry (If Applicable)

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12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)
