For the use of a Registered Medical Practitioner or a Hospital or a Laboratory or a Specialist only

# Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules IP

**Pantopax™ DSR**
Capsules

**COMPOSITION**
**Each hard gelatin capsule contains :**
Pantoprazole Sodium IP
Eq. to Pantoprazole 40 mg
(as gastro-resistant pellets)
Domperidone IP 30 mg
(as prolonged-release pellets)
**Colours:** Lake of Indigo Carmine &
Lake of Sunset Yellow FCF
Approved colours used in hard gelatin capsule shells.

**PHARMACEUTICAL FORM**
Hard Gelatin Capsule.

**THERAPEUTIC INDICATION**
Indicated for the treatment of Gastrooesophageal Reflux Disease (GERD).

**DOSAGE AND ADMINISTRATION**
The recommended dose is 1 capsule once daily or as directed by the Physician.
Method of administration: For oral use.
The capsules should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

**CONTRAINDICATIONS**
Contraindicated if hypersensitivity to the Pantoprazole, Domperidone or any other Excipients of the Formulation.
**Domperidone is Contraindicated in the Following Situations:**
In patients with moderate or Severe Hepatic Impairment.
In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant Electrolyte Disturbances or underlying cardiac diseases such as congestive heart failure. Co-administration with the QT-Prolonging drugs, at the exception of Apomorphine; and co-administration with potent CY3A4 inhibitors (regardless of their QT Prolonging effects).
Prolactin-releasing Pituitary Tumour (Prolactinoma); and Renal Impairment.
Domperidone should not be used when stimulation of gastric motility could be harmful: Gastro-intestinal Haemorrhage, Mechanical Obstruction or Perforation.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**
**Pantoprazole**
**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.
**Combination therapy:** In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.
The 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.
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.
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.
Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile.
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 (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
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. 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.
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.
Increased Chromogranin A (CgA) level may interfere with investigations for Neuroendocrine Tumours. To avoid this interference, Pantoprazole should be stopped for at least 5 days before CgA measurements.
**Domperidone**
**Precautions for use:** Patients with rare hereditary problems of Galactose Intolerance, Total Lactase deficiency or Glucose-Galactose malabsorption should not take this medicine.
Use in infants: Neurological side effects are rare. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.
**Renal Impairment:** The elimination half-life of Domperidone is prolonged in Severe Renal Impairment. For repeated administration, the dosing frequency of Domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.
**Cardiovascular effects:** Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.
Domperidone should be used at the lowest effective dose in adults and children.
Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant Electrolyte Disturbances (Hypokalaemia, Hyperkalaemia, Hypomagnesaemia), or Bradycardia, or in patient with underlying cardiac diseases such as Congestive Heart Failure due to increased risk of Ventricular Arrhythmia. Electrolyte disturbances (Hypokalaemia, Hyperkalaemia, Hypomagnesaemia) or Bradycardia are known to be conditions increasing the Proarrythmic risk.
**Use with Apomorphine:** Domperidone is contra-indicated with QT prolonging drugs including Apomorphine, unless the benefit of the co-administration with Apomorphine outweighs the risks, and only if the recommended precautions for co-administration. Treatment with Domperidone should be stopped if signs or symptoms occur that may be associated with Cardiac Arrhythmia, and the patient should consult their physician. Patient should be advised to promptly report any cardiac symptoms.

**DRUG INTERACTION**
**Pantoprazole**
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 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.
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.
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.
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.
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.
**Domperidone**
Concomitant administration of anticholinergic drugs may antagonize the anti-dyspeptic effect of Domperidone. The main metabolic pathway of Domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of Domperidone.
Separate in vivo interaction studies with oral Ketoconazole or oral Erythromycin in healthy subjects confirmed a marked inhibition of Domperidone's CYP3A4-mediated first-pass metabolism by these drugs. With the combination of oral Domperidone 10 mg four times daily and ketoconazole 200 mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of Domperidone 10 mg four times daily and oral Erythromycin 500 mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of Domperidone at the steady state were increased approximately three-fold in each of these interaction studies. In these studies, Domperidone Monotherapy at 10 mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (Ketoconazole study) and 2.5 msec (Erythromycin study), while Ketoconazole Monotherapy (200 mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.
Use with Potent CYP3A4 Inhibitors: Co-administration with oral Ketoconazole, Erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

**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.
There are limited post-marketing data on the use of Domperidone in pregnant women. Domperidone is not Recommended in Pregnancy.
Breast-feeding
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.
Studies have shown that Domperidone enters breast milk. It is not known whether this is harmful to the newborn. Therefore, breast feeding is not recommended for mothers who are taking Domperidone.
**Fertility**
No evidence of impaired fertility following the administration of Pantoprazole in animal studies.

**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.
Domperidone has no or negligible influence on the ability to drive or use machines.

**UNDESIRABLE EFFECTS / ADVERSE DRUG REACTIONS**
**Proton Pump Inhibitors Associated Acute Kidney Injury :** Acute Kidney Injury has been reported with the use of Proton Pump inhibitors (PPIs) including Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole etc.
The most frequently occurring adverse reactions, occurring at a rate of >2% , in patients on oral Pantoprazole (20mg or 40 mg ) were Headache, Diarrhea, Nausea, Abdominal Pain, Vomiting Flatulence, Dizziness and Arthralgia. Additional adverse reaction that were reported for Pantoprazole with a frequency of <2% were Allergic reaction, Pyrexia, Photosensitivity reaction, Facial Edema, Constipation, Dry, mouth Hepatitis, Eeucopenia, Thrombocytopenia, elevated CK (Creatine Kinese) generalized Edema, elevated triglycerides, elevated liver enzymes, Myalgia, Depression, Vertigo, Urticaria, Rash, Pruitus and blurred Vision.
In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions included URI, Headache, Fever, Diarrhea, Vomiting, Rash and abdominal pain. Additional adverse reactions reported for Pantoprazole in pediatric patients with frequency of <4% were allergic reaction, Facial edema, Constipation, Flatulence, Nausea, Elevated Triglycerides, Elevated liver Enzymes, Elevated CK (Creatine Kinase), Arthralgia, Myalgia, Dizziness, Vertigo and urticaria. Adverse reactions not reported in pediatric patients but are considered relevant to pediatric patients are photosensitivity reaction Dry Mouth, Hepatitis, Thrombocytopenia, Generalized edema, Depression, Pruritus, Leucopenia, and Blurred Vision.
Adverse reactions identified during post approval use of Pantoprazole were Asthenia, Fatigue, Malaise, Pancytopenia, Agranulocytosis, Anaphylaxis (including Anaphylactic Shock), Clostridium difficile associated Diarrhea, Weight changes, Hyponatremia, Hypomagnesemia, Severe Dermatologic reactions (some fatal), including Erythema Multiforme, Stevens-Johnsons Syndrome, and Toxic Epidermal Necrolysis (TEN, some fatal), and Angioedema (Quincke's edema), Rhabdonmyolysis, Bone Fracture, Ageusia, Dysgeusiaa, interstitial nephritis, Hepatocellular Damage leading to Jaundice and Hepatic Failure, Hallucination and Confusion, Insomnia, and Somnolence.
**Domperidone**
**Immune System Disorder:** Very rare; Allergic reaction.
**Endocrine Disorder:** Rare; Increased Prolactin Levels.
**Nervous System Disorders:** Very rare; Extra Pyramidal side Effects.
**GI Disorders:** Rare Gastro-Intestinal disorders including very rare transient Intestinal Cramps.
**Skin and Subcutaneous Tissue Disorders:** Very rare; Urticaria.
**Reproductive System and Breast Disorders:** Rare; Galactorrhoea, Gynaecomastia, Amenorrhoea.
As the hypophysis is outside the blood brain barrier, Domperidone may cause an increase in Prolactin levels. In rare cases this Hyperprolactinaemia may lead to Neuroendrocrinological side effects such as Galactorrhoea, Gynaecomastia and Amenorrhoea. Extrapyramidal side effects are exceptional in adults. These side effects reverse spontaneously and completely as soon as treatment is stopped.

**OVERDOSE**
Systemic exposure with up to 240mg administered intravenously over 2 minutes were well tolerated. As Pantoprazole is extensively protein bound, it is not readily Dialysable. Single oral doses of Pantoprazole at 709mg/kg, 798mg/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.
Overdose has been reported primarily in infants and children. Symptoms of Overdosage may include agitation, altered consciousness, convulsion, Disorientation, Somnolence and Extrapyramidal reactions. There is no specific antidote to Domperidone; but in the event of overdose, gastric lavage as well as the administration of Activated Charcoal may be useful. Anticholinergic, Anti-parkinson drugs may be helpful in controlling the Extrapyramidal reactions.

**PHARMACOLOGICAL PROPERTIES**
Pharmacotherapeutic group: Drugs for acid-related disorders, Proton Pump Inhibitor and Propulsives.
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. 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.
Domperidone, is a Dopamine Antagonist with Anti-Emetic properties. Domperidone does not readily cross the blood-brain barrier. In Domperidone users, especially in adults, extra-pyramidal side effects are very rare, but Domperidone promotes the release of Prolactin from the pituitary. Its Anti-emetic effect may be due to a combination of peripheral (Gastrokinetic) effects and antagonism of central Dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area Postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of Domperidone on dopamine receptors. Studies in humans have shown oral Domperidone to increase lower esophageal pressure, improve Antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

**PHARMACOKINETIC PROPERTIES**
**Absorption**
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. The absolute bioavailability from the tablet was found to be about 77 %.
In fasting subjects, Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral Domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although Domperidone`s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastrointestinal complaints should take Domperidone 15 to 30 minutes before a meal. Reduced gastric acidity impairs the absorption of Domperidone.
**Distribution**
Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.
Domperidone is 91% to 93% bound to plasma proteins.
Metabolism
Pantoprazole is extensively metabolized in the liver through the Cytochrome P450 (CYP) system.
Domperidone undergoes rapid and extensive hepatic metabolism by Hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of CYP450 involved in the N-dealkylation of Domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in Domperidone aromatic Hydroxylation.
Excretion
Renal elimination represents the major route of excretion (about 80 %) for the metabolites of Pantoprazole, the rest is excreted with the Faeces.
Urinary and fecal excretions amount to 31% and 66% of the oral Domperidone dose, respectively. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects, but is prolonged in patients with Severe Renal Impairment.

INCOMPATIBILITY
Not applicable.

**PACKING INFORMATION**
Refer on carton

**STORAGE INSTRUCTIONS**
Store protected from light & moisture,
at a temperature not exceeding 25°C.

Keep all medicines out of reach of children.

Capsule should be swallowed whole and
not opened, chewed or crushed.

Manufactured by: Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of **Akums Drugs & Pharmaceuticals Ltd.**)
Vill. Manakpur, P.O. Lodhimajra, Baddi-173 205,
Distt.-Solan, (H.P.)

Paxole™ PHARMA

**Marketed By:**
**PAXOLE PHARMA PVT LTD**
#80/3, Old Madras Road, KR Puram, Bangalore,
Karnataka-560016
Email: info@paxole.com, Web: www.paxole.com
TM - Trademark under registration

20288973