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

PANSPED DSR

1. Generic Name

Pantoprazole Gastro-Resistant and Domperidone Prolonged –Release Capsules I.P.

2. Qualitative and quantitative Composition:

Each hard gelatin capsule contains:

Pantoprazole Sodium I.P eq to.

Pantoprazole ……. 40 mg

(as gastro resistant pellets)

Domperidone I.P. ……..30 mg

(as prolonged release pellets)

Colour: lake of indigo carmine & lake of sunset Yellow FCF

Approved colours used in capsule shell.

The excipients used are Mannitol, Crospovidone, Sodium Carbonate Anhydrous, Hydroxypropylcellulose, Calcium Stearate, Hydroxypropylmethylcellulose, Titanium Dioxide, Propylene Glycol, Triethyl Citrate, Eudragit, Talc, Lactose, Ferric Oxide Red, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Hard Gelatin Capsule

Strength: Pantoprazole Sodium 40 mg and Domperidone 30 mg.

4. Clinical particulars

4.1. Therapeutic indication

For gastric ulcer, duodenal ulcer, Zollinger-Ellison-syndrome, and Gastro-esophageal reflux diseases.

4.2. Posology and method of administration

Posology

Pantoprazole

Adults and adolescents 12 years of age and above

Reflux oesophagitis.

One tablet of Pantoprazole sodium 40mg per day. In individual cases the daily dose may be doubled (increase to 2 tablets Pantoprazole sodium 40mg 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:

The following combinations have been shown to be effective:

(a) Pantoprazole sodium 40 mg twice daily,
plus 1000 mg amoxicillin twice daily
and 500 mg clarithromycin twice daily

(b) Pantoprazole sodium 40 mg twice daily,
plus 400-500 mg metronidazole (or 500 mg tinidazole) twice daily
and 250-500 mg clarithromycin twice daily

(c) Pantoprazole sodium 40 mg twice daily
plus 1000 mg amoxicillin twice daily
and 400-500 mg metronidazole (or 500 mg tinidazole) twice daily

In combination therapy for eradication of H. pylori infection, the second Pantoprazole sodium 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 sodium monotherapy:

Treatment of gastric ulcer

One tablet of Pantoprazole sodium 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets of Pantoprazole sodium 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 sodium 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole sodium 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 hypersecretory conditions patients should start their treatment with a daily dose of 80mg (2 tablets of Pantoprazole sodium 40mg). Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160mg pantoprazole per day 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

Elderly:

No dose adjustment is necessary in elder people.

Paediatric population:

Pantoprazole sodium 40 mg is not recommended for use in children below twelve years of age because of limited data on safety and efficacy in this age group.

Renal Impairment

No dose adjustment is necessary in patients with impaired renal function. Pantoprazole sodium 40mg 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 sodium 40mg in combination treatment for these patients.

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 sodium 40mg 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 sodium 40mg in combination treatment of these patients.

Domperidone

Domperidone Tablets should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

It is recommended to take oral Domperidone before meals. If taken after meals, absorption of the drug is somewhat delayed.

Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted, and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

Usually, the maximum treatment duration should not exceed one week.

Adults and adolescents (12 years of age and older and weighing 35 kg or more):

One 10mg tablet up to three times per day with a maximum dose of 30mg per day.

Hepatic Impairment

Domperidone Tablets are contraindicated in moderate or severe hepatic impairment. Dose modification in mild hepatic impairment is however, not needed.

Renal Impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of Domperidone Tablets should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric population

The efficacy of Domperidone Tablets in children less than 12 years of age has not been established.

The efficacy of Domperidone Tablets in adolescents 12 years of age and older and weighing less than 35 kg has not been established.

Method of administration

Recommended dose is 1 capsule to be administered once daily for 4 to 8 weeks.

Pansped DSR capsules may be administered with or without food. The capsules should be swallowed whole with water and not to be opened, chewed, or crushed.

Or, as prescribed by the physician.

4.3. Contraindications

Pansped-DSR Capsules are contraindicated in the following:

- Patients with known hypersensitivity to pantoprazole or to any substituted benzimidazole derivative or to domperidone or to any component of the formulation.
- In patients receiving rilpivirine-containing products.
- Prolactin-releasing pituitary tumor (prolactinoma).
- In patients with gastrointestinal hemorrhage, mechanical obstruction, or perforation (i.e., when stimulation of the gastric motility could be harmful).
- 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 (hypokalemia, hyperkalemia, hypomagnesemia) or underlying cardiac disease such as congestive heart failure (CHF).
- Co-administration with QT-prolonging drugs.
- Co-administration with potent CYP3A4 inhibitors.

4.4. Special warnings and precautions for use

<u>Pantoprazole</u>

Presence of Gastric Malignancy: In adults, symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a pantoprazole.

Acute Interstitial Nephritis: Acute interstitial nephritis has been observed in patients taking pantoprazole. Acute interstitial nephritis may occur at any point during pantoprazole therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Clostridium Difficile-Associated Diarrhea (CDAD): Published observational studies suggest that pantoprazole therapy may be associated with an increased risk of CDAD, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.

Risk of Bone Fractures: Proton pump inhibitors (PPIs), 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 recognized risk factors. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. 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.

Cutaneous and Systemic Lupus Erythematosus: Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. The occurrence of CLE with previous PPI treatment may increase the risk of CLE with other PPIs. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. The majority of patients presented with rash. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and pantoprazole

therapy should be stopped immediately. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks.

Cyanocobalamin (Vitamin B12) Deficiency: Generally, daily treatment with any acid-suppressing medication over a long period of time (e.g., longer than 3 years) may lead to malabsorption of vitamin B12 caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), monitoring of magnesium levels prior to initiation of PPI treatment and periodically thereafter should be considered.

Domperidone

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.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolongation drugs or CYP3A4 inhibitors.

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 patients with underlying cardiac diseases such as congestive heart failure (CHF) due to increased risk of ventricular arrhythmia. Electrolyte disturbances or bradycardia are known to be conditions increasing the proarrhythmic risk. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms.

Use with Apomorphine: Domperidone is contraindicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks.

Use in Infants and Children: Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

4.5. Drugs interactions

Pantoprazole

Antiretroviral Drugs: The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

- Decreased exposure of some antiretroviral drugs (e.g., rilpivirine atazanavir, and nelfinavir) when used concomitantly with pantoprazole may reduce antiviral effect and

promote the development of drug resistance. Concomitant use of rilpivirine-containing products with pantoprazole is contraindicated. Also, concomitant use of nelfinavir with pantoprazole should be avoided.

- Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity.
- There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.

Coumarin Anticoagulants/Warfarin: There have been post-marketing reports of increased international normalized ratio (INR) and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Monitor INR and prothrombin time and adjust the dose of warfarin, if needed, to maintain the target INR range.

Clopidogrel: Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of pantoprazole therapy may be considered in some patients receiving high dose of methotrexate.

Drugs for Which Gastric pH Can Affect Bioavailability (iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, and ketoconazole): Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may reduce absorption of other drugs where gastric pH is an important determinant of their bioavailability.

Mycophenolate Mofetil (MMF): Co-administration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving pantoprazole therapy and MMF. Use pantoprazole with caution in transplant patients receiving MMF.

Drug/Laboratory Tests Interactions

False Positive Urine Tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole. An alternative confirmatory method should be considered to verify positive results.

Increased Chromogranin A (CgA) Level: Increase in CgA may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of pantoprazole treatment.

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.

There is increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

1) Concomitant use of the following drugs is contraindicated.

i. QTc-prolonging medicinal products:
- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine).
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antipsychotics (e.g., haloperidol, pimozide, sertindole).
- Certain antidepressants (e.g., citalopram, escitalopram).
- Certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin).
- Certain antifungal agents (e.g., pentamidine).
- Certain antimalarial agents (e.g., halofantrine, lumefantrine).
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride).
- Certain antihistaminics (e.g., mequitazine, mizolastine).
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine).
- Other medicines (e.g., bepridil, diphemanil, methadone)

ii. Potent CYP3A4 inhibitors (regardless of their QT prolonging effects):
- Protease inhibitors.
- Systemic azole antifungals.
- Some macrolides (e.g., erythromycin, clarithromycin, and telithromycin).

2) Concomitant use of the following drugs is not recommended.

- Moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and some macrolides).

3) Concomitant use of the following drugs requires caution.

- Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: Azithromycin and roxithromycin.

Ketoconazole/Erythromycin and QTc Prolongation: Separate in vivo pharmacokinetic/pharmacodynamic 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 (as both of these drugs significantly inhibit CYP3A4 enzyme). Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies, concomitant use of domperidone and ketoconazole or erythromycin resulted in increase in QTc, over the observation period.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnant Women

Pantoprazole: Pregnancy Category C; **Domperidone:** Pregnancy Category C. Reproduction studies have been performed in rats at oral doses up to 88- times the recommended human dose and in rabbits at oral doses up to 16-times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

There are however, no adequate and well controlled studies available for use of pantoprazole with domperidone combination therapy in pregnant women. Because animal reproduction studies are not always predictive of human response, P-RD Capsules should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Lactating Women

Animal studies have shown that pantoprazole and its metabolites are excreted in the milk. Excretion of pantoprazole in human milk has also been reported (insufficient information). However, the clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Similarly, with pantoprazole, a risk to the newborns/infants cannot be excluded.

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

Pantosped-DSR Capsules should not be used during breast feeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue/abstain from therapy, taking into account the benefit of the drug to the mother.

Paediatric Patients

Safety and efficacy of pantoprazole with domperidone combination therapy has not been established in paediatric patients. Thus, Pantosped-DSR Capsules are not recommended for use in children and adolescents below 18 years of age.

Geriatric Patients

No overall differences in safety or effectiveness were observed between elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be given the same dose as recommended for adults. No dose adjustment is necessary in these patients.

Renal Impairment Patients

Dosage modification is not necessary when pantoprazole is administered to patients with impaired renal function. On repeated administration, the elimination half-life of domperidone is prolonged in patients with severe renal impairment. Pantosped-DSR Capsules can be administered in patients with mild to moderate renal dysfunction. However, in patients with severe renal impairment, Pantosped-DSR Capsules should be used with caution and dose/dosage frequency may need to be reduced depending on the severity of the renal dysfunction.

Hepatic Impairment Patients

In patients with severe liver impairment, a daily dose of pantoprazole 20 mg should not be exceeded. With domperidone, no dosage adjustment is necessary in patients with mild hepatic impairment. Thus, Pantosped-DSR Capsules can be administered in patients with mild hepatic dysfunction. If used in these patients, the liver enzymes should be monitored regularly, particularly on long-term therapy. In the case of a rise in liver enzymes, the treatment should be discontinued. Pantosped-DSR Capsules are contraindicated in patients with moderate or severe hepatic impairment.

4.7. Effects on ability to drive and use machines.

Both, pantoprazole and domperidone have no or negligible influence on the ability to drive and use machines. However, adverse reactions such as dizziness and visual disturbances may occasionally occur in patients on PPIs drug therapy. If affected, patients should not drive or use machines.

4.8. Undesirable effects

Pantoprazole

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in clinical practice.

Common adverse reactions reported with pantoprazole therapy in clinical trials with frequency > 2% include: Headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.

Additional adverse reactions reported in clinical trials with a frequency of ≤ 2% include:

Body as a Whole: Allergic reaction, pyrexia, photosensitivity reaction, facial edema.

Gastrointestinal: Constipation, dry mouth, hepatitis.

Hematologic: Leukopenia, thrombocytopenia.

Metabolic/Nutritional: Elevated creatine kinase (CK), generalized edema, elevated triglycerides, elevated liver enzymes.

Musculoskeletal: Myalgia.

Nervous: Depression, vertigo.

Skin and Appendages: Urticaria, rash, pruritus.

Special Senses: Blurred vision.

Post-Marketing Experience

Acute kidney injury as an adverse drug reaction reported with the use of proton pump inhibitors. The following adverse reactions have been identified during post-approval use of pantoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General Disorders and Administration Conditions: Asthenia, fatigue, malaise.

Hematologic: Pancytopenia, agranulocytosis.

Hepatobiliary Disorders: Hepatocellular damage leading to jaundice and hepatic failure.

Immune System Disorders: Anaphylaxis (including anaphylactic shock), SLE.

Infections and Infestations: Clostridium difficile-associated diarrhea.

Investigations: Weight changes.

Metabolism and Nutritional Disorders: Hyponatremia, hypomagnesemia.

Musculoskeletal Disorders: Rhabdomyolysis, bone fracture.

Nervous System: Ageusia, dysgeusia.

Psychiatric Disorders: Hallucination, confusion, insomnia, somnolence.

Renal and Urinary Disorders: Interstitial nephritis.

Skin and Subcutaneous Tissue Disorders: Severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema (Quincke's edema) and CLE.

Domperidone

Central Nervous System: As the pituitary gland is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped. Other central nervous system-related effects of convulsion, agitation and somnolence also are very rare and primarily reported in infants and children.

The adverse drug reactions are ranked below by frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000), not known (cannot be estimated from available data).

General Disorders: Uncommon: Asthenia.

Immune System Disorder: Not known: Anaphylactic reactions including anaphylactic shock and angioedema.

Psychiatric Disorders: Uncommon: Anxiety, loss of libido; Not known: Agitation, nervousness.

Nervous System Disorders: Uncommon: Somnolence, headache; Not known: Extrapyramidal disorder, convulsions.

Eye Disorders: Not known: Oculogyric crisis.

Cardiac Disorders: Not known: Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, sudden cardiac death.

Gastrointestinal Disorders: Common: Dry mouth; Uncommon: Diarrhoea.

Skin and Subcutaneous Tissue Disorders: Uncommon: Rash, pruritus; Not known: Urticaria, angioedema.

Reproductive System and Breast Disorders: Uncommon: Breast pain, breast tenderness, galactorrhoea; Not known: Gynaecomastia, amenorrhoea.

Renal and Urinary Disorders: Not known: Urinary retention.

Investigations: Not known: Abnormal liver function test, increased blood prolactin.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Pantoprazole

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

Domperidone

Symptoms of domperidone overdose may include agitation, altered consciousness, convulsions, 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. Close medical supervision and supportive therapy is recommended. Anticholinergic, antiparkinsonian drugs may be helpful in controlling the extrapyramidal reactions.

5. Pharmacological properties

5.1. Mechanism of Action

Pantoprazole

Pantoprazole is a proton pump inhibitor (PPI) class of antisecretory agent. Pantoprazole is a lipophilic weak base that crosses the parietal cell membrane and enters the acidic parietal cell canaliculus where it becomes protonated, producing the active metabolite sulfenamide. Sulfenamide forms an irreversible covalent bond with two sites of the H+/K+-ATPase enzyme located on the gastric parietal cell. Thus, pantoprazole suppresses the final step in gastric acid (hydrochloric acid – HCl) production by covalently binding to the H+/K+-ATPase enzyme (also called as proton pump) system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the H+/K+-ATPase results in duration of antisecretory effect that persists longer than 24 hours.

Domperidone

Domperidone is a dopamine receptor (D2) antagonist. Domperidone act predominantly on peripheral dopamine receptors and produces anti-emetic and gastrokinetic effects. Domperidone does not readily cross the blood-brain barrier (BBB). Thus, in domperidone users, especially in adults, extrapyramidal side effects are very rare (unlike metoclopramide). Anti-emetic effect of domperidone is due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors (D2) in the chemoreceptor trigger zone (CTZ), which lies outside the BBB in the area postrema.

Oral domperidone also increases lower esophageal sphincter (LES) pressure, thus, improve antroduodenal motility and accelerate gastric emptying.

5.2. Pharmacodynamic properties

Pantoprazole

With a single oral dose of 20 to 80 mg of pantoprazole, a dose-dependent decrease in gastric acid secretion occurs. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

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 receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, and gastrin).

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.

Domperidone

Prokinetic Effect: The prokinetic (gastrokinetic) properties of domperidone are related to its peripheral dopamine receptor blocking action.

Antiemetic Effect: Domperidone produces antiemetic effect by blocking dopamine receptors (D2) peripherally. Inhibition of peripheral D2 receptor signaling prevents or relieves various GI symptoms, such as nausea and vomiting, and also relieves reflux and other symptoms associated with upper GI disorders.

5.3. Pharmacokinetic properties

Pantoprazole

Absorption: Like other PPIs, pantoprazole is an acid-labile drug and therefore, administered orally in the form of gastro-resistant pellets. Absorption of pantoprazole, therefore, begins in the intestine only after the pellets leave the stomach.

After administration of a single or multiple oral doses of pantoprazole 40 mg, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C_{max} was 2.5 mcg/ml. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increases in a dose-dependent manner (with dose range from 10 to 80 mg). Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%.

Effect of Antacid/Food: Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution: The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 liters, distributing mainly in extracellular fluid. The plasma protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Excretion: Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole, the rest is excreted with the faeces. There is no renal excretion of unchanged pantoprazole. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with sulphate. Following oral administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

Domperidone

Pharmacokinetics of domperidone in prolonged-release formulation is not available. Conventional formulation of domperidone (i.e., immediate release) has following pharmacokinetic properties:

Absorption: Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hour after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut and liver.

Effect of Food: Domperidone's bioavailability is enhanced in normal subjects when taken after a meal. The time of peak absorption is slightly delayed and the AUC somewhat increased when domperidone is taken after a meal.

Distribution: Oral domperidone does not appear to accumulate or induce its own metabolism. The peak plasma concentration (C_{max}) of 18 ng/ml to 21 ng/ml occurs 1.5 hours (T_{max}) after the oral dose. Domperidone is 91 to 93% bound to plasma proteins. Distribution studies with domperidone have shown wide tissue distribution, but low brain concentration.

Metabolism: 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 cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion: After oral dose, domperidone is excreted mainly by renal (31%) and biliary (66%) routes. 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 insufficiency.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis: In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with pantoprazole doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50 kg person dosed with 40 mg/day. In the gastric fundus, treatment with 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment with 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day of pantoprazole, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment with 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment with 5 to 150 mg/kg/day also produced gastric-fundic ECL cell hyperplasia.

A 26-week p53 +/-transgenic mouse carcinogenicity study was not positive.

Mutagenesis: Pantoprazole was positive in the in vitro human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the in vitro Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the in vivo rat liver DNA covalent binding assay. Pantoprazole was negative in the in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the in vitro AS52/GPT mammalian cell-forward gene mutation assay, the in vitro thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the in vivo rat bone marrow cell chromosomal aberration assay.

Impairment of Fertility: There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the

recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

Teratogenicity: Reproduction studies have been performed in rats at oral pantoprazole doses up to 450 mg/kg/day (about 88 times the recommended human dose based on body surface area) and in rabbits at oral doses up to 40 mg/kg/day (about 16 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals. The studies have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

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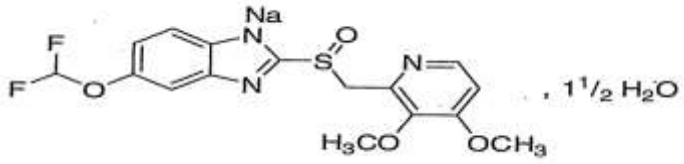
Safety margins in *in vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45-fold. In *in vivo* models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4ng/ml, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day).

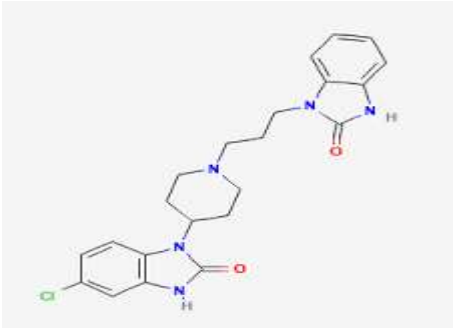
At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits. Development abnormalities observed in rats at a high exposure. Risk of carcinogenicity, mutagenicity or sensitisation cannot be excluded.

7. Description

Pantoprazole Sodium is sodium 5-(difluromethoxy) 2[[(3, 4-dimethoxy-pyridin-2-yl)methyl]sulphinyl]-benzimidazol-1-ide,sesquihydrate having molecular formula of $C_{16}H_{14}F_2N_3NaO_4S$, 1.5 H_2O molecular weight is 432.4 the chemical structure is:



Domperidone is a dopamine antagonist with anti-emetic properties. Chemically it is 5 Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one. It has an empirical formula of $C_{22}H_{24}ClN_5O_2$ and molecular weight of 425.9. The structure is as follow.



8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

PANSPED DSR is available as strip of 10 capsules.

8.4. Storage and handing instructions.

Store below 25 º C, protected from light and moisture.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Haridwar-249 403, Uttarakhand

11. Details of permission or licence number with date

MNB/05/183 issued on 09.11.2011.

12. Date of revision

NA

MARKETED BY

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TORRENT PHARMACEUTICALS LTD.

IN/PANSPED DSR 40/30 mg/FEB 2025/01/PI