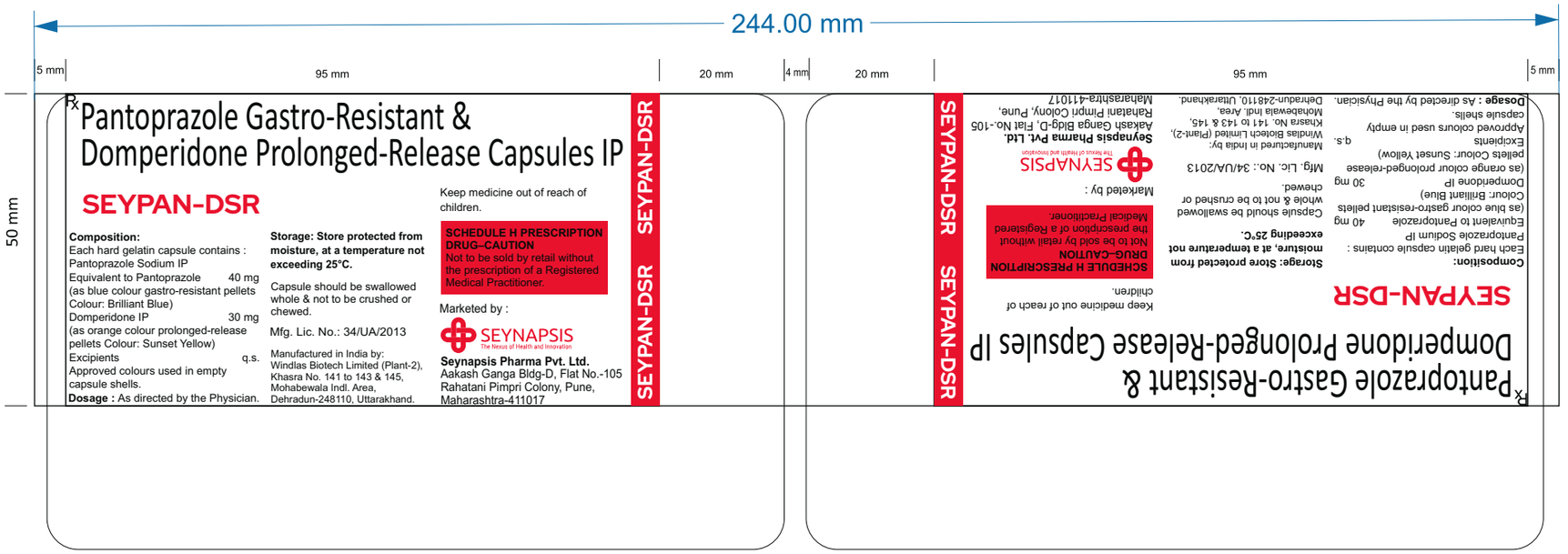
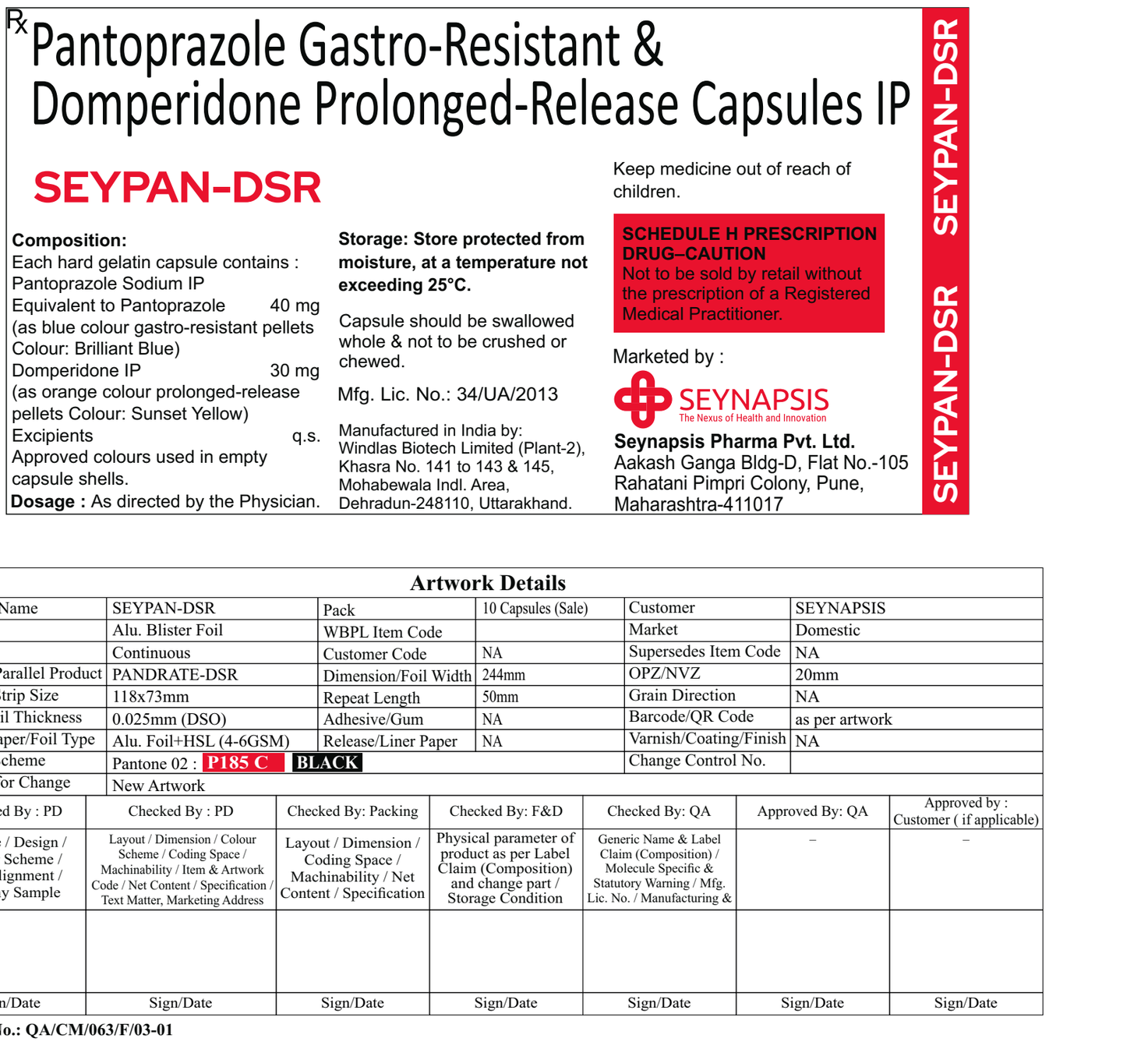
Artwork Details					
Product Name	SEYPAN-DSR	Pack	10x10 Capsules (Sale)	Customer	SEYNAPSIS
Item	Unit Carton	WBPL Item Code		Market	Domestic
Design	LBTO	Customer Code	NA	Supersedes	NA
Layout/Parallel Product	RABINOF-DSR	Dimension/Foil Width	121x78x76 mm (ID)	Item CodeOPZ/NVZ	As per Artwork
Folded/Strip Size	NA	Repeat Length	NA	Grain Direction	Perpendicular to pasting flap
GSM/Foil Thickness	320 GSM	Adhesive/Gum	NA	Barcode/QR Code	NA
Board/Paper /Foil Type	FBB	Release/Liner Paper	NA	Varnish/Coating/Finish	UV
Colour Scheme	04 (CMYK)			Change Control No.	
Reason for Change	New				

Prepared By: PD	Checked By:PD	Checked By: Packing	Checked By: F&D	Checked By: QA	Approved By: QA	Approved by: Customer (if applicable)
Keyline / Design / Colour Scheme / Text Alignment / Dummy Sample	Layout / Dimension / Colour Scheme / Coding Space / Machinability / Item & Artwork Code / Net Content / Specification / Text Matter, Marketing Address	Layout / Dimension / Coding Space / Machinability / Net Content / Specification	Physical parameter of product as per Label Claim (Composition) and change part / Storage Condition	Generic Name & Label Claim (Composition) / Molecule Specific & Statutory Warning / Mfg. Lic. No. / Manufacturing &	--	--
Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date

Format No.: QA/CM/063/F/03-01





℞ Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules IP

SEYPAN-DSR

Composition:
Each hard gelatin capsule contains :
Pantoprazole Sodium IP
Equivalent to Pantoprazole 40 mg
(as blue colour gastro-resistant pellets
Colour: Brilliant Blue)
Domperidone IP 30 mg
(as orange colour prolonged-release
pellets Colour: Sunset Yellow)
Excipients q.s.
Approved colours used in empty
capsule shells.
Dosage : As directed by the Physician.

Storage: Store protected from moisture, at a temperature not exceeding 25°C.

Capsule should be swallowed whole & not to be crushed or chewed.

Mfg. Lic. No.: 34/UA/2013

Manufactured in India by:
Windlas Biotech Limited (Plant-2),
Khasra No. 141 to 143 & 145,
Mohabewala Indl. Area,
Dehradun-248110, Uttarakhand.

Keep medicine out of reach of children.

SCHEDULE H PRESCRIPTION DRUG–CAUTION
Not to be sold by retail without the prescription of a Registered Medical Practitioner.

Marketed by :

SEYNAPSIS
The Nexus of Health and Innovation

Seynapsis Pharma Pvt. Ltd.
Aakash Ganga Bldg-D, Flat No.-105
Rahatani Pimpri Colony, Pune,
Maharashtra-411017

SEYPAN-DSR
SEYPAN-DSR

Artwork Details

Product Name	SEYPAN-DSR	Pack	10 Capsules (Sale)	Customer	SEYNAPSIS
Item	Alu. Blister Foil	WBPL Item Code		Market	Domestic
Design	Continuous	Customer Code	NA	Supersedes Item Code	NA
Layout/Parallel Product	PANDRATE-DSR	Dimension/Foil Width	244mm	OPZ/NVZ	20mm
Folded/Strip Size	118x73mm	Repeat Length	50mm	Grain Direction	NA
GSM/Foil Thickness	0.025mm (DSO)	Adhesive/Gum	NA	Barcode/QR Code	as per artwork
Board/Paper/Foil Type	Alu. Foil+HSL (4-6GSM)	Release/Liner Paper	NA	Varnish/Coating/Finish	NA
Colour Scheme	Pantone 02 : P185 C BLACK			Change Control No.	
Reason for Change	New Artwork				

Prepared By : PD	Checked By : PD	Checked By: Packing	Checked By: F&D	Checked By: QA	Approved By: QA	Approved by : Customer (if applicable)
Keyline / Design / Colour Scheme / Text Alignment / Dummy Sample	Layout / Dimension / Colour Scheme / Coding Space / Machinability / Item & Artwork Code / Net Content / Specification / Text Matter, Marketing Address	Layout / Dimension / Coding Space / Machinability / Net Content / Specification	Physical parameter of product as per Label Claim (Composition) and change part / Storage Condition	Generic Name & Label Claim (Composition) / Molecule Specific & Statutory Warning / Mfg. Lic. No. / Manufacturing &	–	–
Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date

Format No.: QA/CM/063/F/03-01

Prescribing Information

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

Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules IP

SEYPAN-DSR

1. GENERIC NAME

Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:

Pantoprazole Sodium IP	
Equivalent to Pantoprazole	40 mg
(as blue colour gastro-resistant pellets	
Colour: Brilliant Blue)	
Domperidone IP	30 mg
(as orange colour prolonged-release pellets	
Colour: Sunset Yellow)	
Excipients	q.s.

Approved colours used in empty capsule shells.

3. DOSAGE FORM AND STRENGTH

Oral Dosage form (Capsules)

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

It is indicated for the treatment of GERD not responding to pantoprazole.

4.2 Posology and method of administration

The recommended dose of Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules is one capsule daily before breakfast.

4.3 Contraindications

Pantoprazole

Pantoprazole capsules are contraindicated in case of hypersensitivity to the active substance, substituted benzimidazoles, or to any of the other excipients of the tablet. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angio-oedema, bronchospasm, acute interstitial nephritis, and urticaria. Proton-pump inhibitors (PPIs), including pantoprazole sodium capsules, are contraindicated with rilpivirine-containing products.

Domperidone

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 QT-prolonging drugs, with the exception of apomorphine
- Co-administration with potent CY3A4 inhibitors (regardless of their QT-prolonging effects)
- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma)
- Renal impairment

Domperidone should not be used when stimulation of gastric motility could be harmful: gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Pantoprazole

Presence of Gastric Malignancy

Symptomatic response to therapy with pantoprazole sodium does not preclude the presence of gastric malignancy. In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis. 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 PPI. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs, including pantoprazole sodium delayed-release capsules. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue pantoprazole sodium delayed-release capsules if acute interstitial nephritis develops.

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was sub-acute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. SLE is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug-induced SLE. Onset of SLE typically occurred within days to years after initiating treatment, primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopaenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving pantoprazole sodium delayed-release capsules , discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4–12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Cyanocobalamin (Vitamin B_{12}) Deficiency

Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (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.

Clostridium difficile-associated Diarrhoea

Published observational studies suggest that PPI therapy such as pantoprazole sodium may be associated with an increased risk of Clostridium difficile-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). 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.

Hypomagnesaemia

Hypomagnesaemia, 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 hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Tumourigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole sodium. In long-term rodent studies, pantoprazole sodium was carcinogenic and caused rare types of gastrointestinal tumours. The relevance of these findings to tumour development in humans is unknown.

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond 1 year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy . Use the shortest duration of PPI therapy appropriate to the condition being treated.

Interference with Investigations for Neuroendocrine Tumours

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false-positive results in diagnostic investigations for neuroendocrine tumours. Healthcare providers should temporarily stop pantoprazole sodium delayed-release tablet treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Interference with Urine Screen for THC

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole sodium delayed-release capsules .

Concomitant Use of Pantoprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Hepatic Impairment

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole sodium, 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.

HIV Protease Inhibitors

Co-administration of pantoprazole sodium 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 PPI is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole sodium dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitors may need to be adjusted.

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

Pantoprazole sodium, like all PPIs, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole sodium may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Domperidone

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During postmarketing 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 QTprolonging drugs or CYP3A4 inhibitors.

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 patients 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. 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, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled.

Use in Infants

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.

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.

4.5 Drug Interactions

Pantoprazole

Pantoprazole sodium is extensively metabolised in the liver via the cytochrome (CY) P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolised with these pathways such as carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyloestradiol did not reveal clinically significant interactions.

An interaction of pantoprazole sodium with other medicinal products or compounds, which are metabolised using the same enzyme system, cannot be excluded. Results from a range of interaction studies demonstrate that pantoprazole sodium 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.

Antacids

There were no interactions with concomitantly administered antacids.

HIV Protease Inhibitors

Co-administration of pantoprazole sodium 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 PPI is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole sodium 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 sodium 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 sodium and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Clopidogrel

Concomitant administration of pantoprazole sodium 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 sodium.

Drugs for Which Gastric pH Can Affect Bioavailability

Pantoprazole sodium causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole sodium may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole, ampicillin esters, iron salts and other medicines such as erlotinib).

False-Positive Urine Tests for THC

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

Methotrexate

Case reports published population pharmacokinetic studies and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high doses; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Medicinal Products That Inhibit or Induce CYP2C19

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole sodium. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole sodium, 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.

Interactions with Investigations of Neuroendocrine Tumours

CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false-positive results in diagnostic investigations for neuroendocrine tumours. Temporarily stop pantoprazole sodium delayed-release tablet treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

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.

Concomitant use of the following substances is contraindicated

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 (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled.

Potent CYP3A4 inhibitors (*regardless of their QT prolonging effects*), i.e:

protease inhibitors

- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin and telithromycin)

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

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.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg 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 10mg four times daily and oral erythromycin 500mg 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 C_{max} and AUC of domperidone at steady state were increased approximately three- fold in each of these interaction studies. In these studies, domperidone monotherapy at 10mg 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 (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

4.6 Use in special populations

Pantoprazole

Patients with Renal Impairment

No dosage adjustment is required in patients with impaired renal function (including dialysis patients).

Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild-to-severe hepatic impairment. In patients with severe liver impairment, the liver enzymes should be monitored during therapy. Doses higher than 40 mg/day have not been studied in patients with hepatic impairment.

Pregnant Women

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of foetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactating Women

Pantoprazole sodium and its metabolites are excreted in the milk of rats. Pantoprazole sodium excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Based on the potential for tumourigenicity shown for pantoprazole sodium in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Paediatric Patients

The safety and effectiveness of pantoprazole sodium for short term treatment (up to 8 weeks) of EE associated with GERD have been established in paediatric patients, 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, pantoprazole sodium is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of pantoprazole sodium for paediatric uses other than EE have not been established.

1 Year Through 16 Years of Age

Use of pantoprazole sodium in paediatric patients, 1 year through 16 years of age, for short-term treatment (up to 8 weeks) of EE associated with GERD is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of pantoprazole sodium for treatment of EE associated with GERD in adults; and b) safety, effectiveness, and pharmacokinetic studies performed in paediatric patients.

Safety of pantoprazole sodium in the treatment of EE associated with GERD in paediatric patients, 1 through 16 years of age, was evaluated in three multicentre, randomised, double-blind, parallel treatment studies, involving 249 paediatric patients, including 8 with EE (4 patients aged 1 year to 5 years; and 4 patients aged 5 years to 11 years). The children aged 1 year to 5 years with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥2) were treated once daily for 8 weeks with one of two dose levels of pantoprazole sodium (approximating 0.6 mg/kg or 1.2 mg/kg). All 4 of these patients with EE were healed (Hetzel Dent score of 0 or 1) at 8 weeks. Because EE is uncommon in the paediatric population, predominantly paediatric patients with endoscopically-proven or symptomatic GERD were also included in these studies. Patients were treated with a range of doses of pantoprazole sodium once daily for 8 weeks. Because these paediatric trials had no placebo, active comparator or evidence of a dose response, the trials were inconclusive regarding the clinical benefit of pantoprazole sodium for symptomatic GERD in the paediatric population. The effectiveness of pantoprazole sodium for treating symptomatic GERD in paediatric patients has not been established.

Although the data from the clinical trials support use of pantoprazole sodium for the short-term treatment of EE associated with GERD in paediatric patients, 1 year through 5 years of age, there is no commercially available dosage formulation appropriate for patients less than 5 years of age.

In a population pharmacokinetic analysis, clearance values in the children aged 1 to 5 years old with endoscopically proven GERD had a median value of 2.4 L/h. Following a 1.2 mg/kg equivalent dose (15 mg for ≤12.5 kg and 20 mg for >12.5 to <25 kg), the plasma concentrations of pantoprazole sodium were highly variable and the median time to peak plasma concentration was 3–6 hours. The estimated AUC for patients, 1 to 5 years old, was 37% higher than for adults receiving a single 40 mg tablet, with a geometric mean AUC value of 6.8 mcg•hr/mL.

Neonates to <1 year of Age

Pantoprazole sodium was not found to be effective in a multicentre, randomised, double-blind, placebo controlled, treatment-withdrawal study of 129 paediatric patients,1 through 11 months of age. Patients were enrolled if they had symptomatic GERD based on medical history and had not responded to non-pharmacologic interventions for GERD for 2 weeks. Patients received pantoprazole sodium daily for 4 weeks in an open-label phase; then, patients were randomised in equal proportion to receive pantoprazole sodium treatment or placebo for the subsequent 4 weeks in a double-blind manner. Efficacy was assessed by observing the time from randomisation to study discontinuation due to symptom worsening during the 4-week treatment-withdrawal phase. There was no statistically significant difference between pantoprazole sodium and placebo in the rate of discontinuation.

In this trial, the adverse reactions that were reported more commonly (difference of ≥4%) in the treated population compared with the placebo population were elevated creatine kinase, otitis media, rhinitis and laryngitis.

In a population pharmacokinetic analysis, the systemic exposure was higher in patients less than 1 year of age with GERD compared with adults who received a single 40 mg dose (geometric mean AUC was 103% higher in pre-term infants and neonates receiving a single dose of 2.5 mg of pantoprazole sodium, and 23% higher in infants, 1 through 11 months of age, receiving a single dose of approximately 1.2 mg/kg). In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03–3.2 L/hr).

These doses resulted in pharmacodynamic effects on gastric but not oesophageal pH. Following once-daily dosing of 2.5 mg of pantoprazole sodium in pre-term infants and neonates, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at the steady state) and in the mean percent time that gastric pH was >4 (from 60% at baseline to 80% at the steady state). Following once-daily dosing of approximately 1.2 mg/kg of pantoprazole sodium in infants 1 through 11 months of age, there was an increase in the mean gastric pH (from 3.1 at baseline to 4.2 at the steady state) and in the mean % time that gastric pH was >4 (from 32% at baseline to 60% at the steady state). However , no significant changes were observed in mean intra-oesophageal pH or % time that oesophageal pH was <4 in either age group.

Because pantoprazole sodium was not shown to be effective in the randomised, placebo-controlled study in this age group, the use of pantoprazole sodium for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Domperidone

Pregnant Women

There are limited Postmarketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses. Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactating Women

Domperidone is excreted in human milk and breastfed 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. A decision should be made whether to discontinue breastfeeding or to discontinue/abstain from domperidone therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Caution should be exercised in case of QTc prolongation risk factors in breastfed infants.

Paediatric Patients

Domperidone is not recommended in cases other than that of nausea and vomiting during cancer therapy. There may be an increased risk for extra-pyramidal reactions in young children because of an incompletely developed blood-brain barrier. Hence Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules are not recommended in paediatric patients.

Geriatric Patients

No special precautions are necessary while recommending Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules to older patients.

4.7 Effects on ability to drive and use machines

Pantoprazole

Pantoprazole sodium 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

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

4.8 Undesirable effects

Pantoprazole

The following serious adverse reactions are described below and elsewhere in the labelling:

- Acute Interstitial Nephritis
- Clostridium difficile-associated Diarrhoea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B12) Deficiency
- Hypomagnesaemia
- Fundic Gland Polyps

Proton pump inhibitor use was found to be associated with increased risks for acute kidney injury.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Safety in nine randomised comparative US clinical trials in patients with GERD included 1,473 patients on oral pantoprazole sodium (20 mg or 40 mg), 299 patients on an H_2 -receptor antagonist, 46 patients on another PPI, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table 1.

Table 1: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of >2%

	Pantoprazole (n=1,473) %	Comparators (n=345) %	Placebo (n=82) %
Headache	12.2	12.8	8.5
Diarrhoea	8.8	9.6	4.9
Nausea	7.0	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3.0	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for pantoprazole sodium in clinical trials with a frequency of ≤2% are listed below by body system:

Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial oedema.

General Disorders at Site of Administration: asthenia, fatigue and malaise, body temperature increased; oedema peripheral.

Gastrointestinal: diarrhoea; nausea/vomiting; abdominal distension and bloating; constipation; dry mouth; abdominal pain and discomfort, hepatitis.

Haematologic: leucopaenia, thrombocytopaenia, pancytopaenia.

Immune System Disorders: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Metabolic/Nutritional: elevated creatine kinase, generalised oedema, elevated triglycerides, liver enzymes (transaminases, gamma-GT) and bilirubin elevated, weight changes, hyperlipidaemias and lipid increase (triglycerides, cholesterol), hypocalcaemia and hypokalaemia.

Musculoskeletal: fracture of the hip, wrist or spine myalgia, arthralgia, muscle spasm.

Psychiatric and Nervous System Disorders: depression (and all aggravations), disorientation (and all aggravations), vertigo, taste disorders, paraesthesia, sleep disorders.

Skin and Appendages: rash/exanthema/eruption, urticaria, pruritus, angio-oedema.

Special Senses: disturbances in vision/blurred vision.

Reproductive System and Breast Disorders: gynaecomastia.

Adverse reactions whose frequency of occurrence is not known but may occur include hyponatraemia, hypomagnesaemia, hallucination; confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence), hepatocellular injury; jaundice; hepatocellular failure, Stevens-Johnson syndrome; Lyell syndrome; erythema multiforme; photosensitivity; and interstitial nephritis.

Paediatric Patients

Safety of pantoprazole sodium in the treatment of EE associated with GERD was evaluated in paediatric patients aged 1 year through 16 years in three clinical trials. Safety trials involved paediatric patients with EE; however, as EE is uncommon in the paediatric population, 249 paediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. All adult adverse reactions to pantoprazole sodium are considered relevant to paediatric patients. In patients aged 1 year through 16 years, the most commonly reported (>4%) adverse reactions include URI, headache, fever, diarrhoea, vomiting, rash, and abdominal pain.

Additional adverse reactions that were reported for pantoprazole sodium in paediatric patients in clinical trials with a frequency of ≤4% are listed below by body system:

Body as A Whole: allergic reaction, facial oedema

Gastrointestinal: constipation, flatulence, nausea

Metabolic/Nutritional: elevated triglycerides, elevated liver enzymes, elevated creatine kinase

Musculoskeletal: arthralgia, myalgia

Nervous: dizziness, vertigo

Skin and Appendages: urticaria

The following adverse reactions seen in adults in clinical trials were not reported in paediatric patients in clinical trials but are considered relevant to paediatric patients: photosensitivity reaction, dry mouth, hepatitis, thrombocytopaenia, generalised oedema, depression, pruritus, leucopaenia, and blurred vision.

Zollinger-Ellison Syndrome

In clinical studies of Zollinger-Ellison syndrome, adverse reactions reported in 35 patients taking pantoprazole sodium 80 mg/day to 240 mg/day for up to 2 years were similar to those reported in adult patients with GERD

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of pantoprazole sodium. 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.

These adverse reactions are listed below by body system:

Gastrointestinal Disorders: fundic gland polyps

General Disorders and Administration Conditions: asthenia, fatigue, malaise

Haematologic: pancytopaenia, agranulocytosis

Hepatobiliary Disorders: hepatocellular damage, leading to jaundice and hepatic failure

Immune System Disorders: anaphylaxis (including anaphylactic shock), systemic lupus erythematosus

Infections and Infestations: Clostridium difficile-associated diarrhoea

Investigations: weight changes

Metabolism and Nutritional Disorders: hyponatraemia, hypomagnesaemia.

Musculoskeletal Disorders: Rhabdomyolysis, bone fracture

Nervous: ageusia, dysgeusia

Psychiatric Disorders: hallucination, confusion, insomnia, somnolence

Renal and Urinary Disorders: interstitial nephritis, acute kidney injury

Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal), angio-oedema (Quincke's oedema) and cutaneous lupus erythematosus.

Domperidone

The safety of domperidone was evaluated in 1,275 patients with dyspepsia, GERD, irritable bowel syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo controlled studies.

Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or Parkinsonism were excluded. The following terms and frequencies are applied: 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).

Where frequency cannot be estimated from clinical trials data, it is recorded as "Not known".

Table 2

System Organ Class	Adverse Drug Reaction Frequency		
	Common	Uncommon	Not known
Immune system disorder			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias Sudden cardia death QTc prolongation Torsade de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticarial angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhea Breast pain Breast tenderness	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

4.9 Overdose

Pantoprazole

Experience in patients taking very high doses of pantoprazole sodium (>240 mg) is limited. Spontaneous Postmarketing reports of overdose are

generally within the known safety profile of pantoprazole sodium.
Pantoprazole sodium is not removed by haemodialysis. In case of overdosage, treatment should be symptomatic and supportive.
Single oral doses of pantoprazole sodium 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.

Domperidone

Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.
Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Pantoprazole

Pantoprazole sodium is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme 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 a duration of anti-secretory effect that persists longer than 24 hours for all doses tested (20–120 mg).

Domperidone

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially 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 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 oesophageal pressure, improve gastroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2. Pharmacodynamic properties

Pantoprazole

Anti-Secretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20–80 mg) pantoprazole sodium in healthy volunteers. Pantoprazole sodium given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole sodium, 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%. Pantoprazole sodium suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion returned to normal within a week after the last dose of pantoprazole sodium; there was no evidence of rebound hypersecretion. In a series of dose-response studies, pantoprazole sodium, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was >3 and >4. Treatment with 40 mg of pantoprazole sodium produced significantly greater increases in gastric pH than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole sodium on median pH from one double-blind crossover study are shown in Table 3.

Table 3: Effect of Single Daily Doses of Oral Pantoprazole Sodium on Intra-Gastric pH

	Median pH on day 7			
Time	**Placebo**	**20 mg**	**40 mg**	**80 mg**
8 a.m. – 8 a.m. (24 hours)	1.3	2.9*	3.8*†	3.9*†
8 a.m. – 10 p.m.(Daytime)	1.6	3.2*	4.4*†	4.8*†
10 p.m. – 8 a.m. (Night-time)	1.2	2.1*	3.0*	2.6*
*Significantly different from placebo †Significantly different from 20 mg				

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of EE in which 682 patients with GERD received 10, 20, or 40 mg of pantoprazole sodium for up to 8 weeks. At 4 weeks of treatment, there was an increase in mean gastrin levels of 7%, 35%, and 72% over pre-treatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole sodium dose groups.
In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pre-treatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole sodium at doses of 40 mg per day during GERD maintenance studies and at 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials. Following short-term treatment with pantoprazole sodium delayed-release capsules , elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole sodium 40–240 mg daily (majority receiving 40–80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years.
In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole sodium at doses of 0.5–200 mg/kg/day resulted in dose-related increases in gastric ECL cell proliferation and gastric neuroendocrine (NE)-cell tumours. Gastric NE-cell tumours in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by PPIs. However, there were no observed elevations in serum gastrin following the administration of pantoprazole sodium at a dose of 0.5 mg/kg/day.
In a separate study, a gastric NE-cell tumour without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole sodium at 5 mg/kg/day and a 9 month off-dose recovery.

Domperidone

Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.
In accordance with ICH-E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90% CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effect were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).
However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day). The largest time- matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5msec (95 % CI: 0.6 to 14.4), respectively.

Clinical study in infants and children 12 years of age and younger

A multicentre, double-blind, randomised, placebo-controlled, parallel-group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomised subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing vomiting episodes during the first 48 hours after the first treatment administration.

5.3. Pharmacokinetic properties

Pantoprazole

Pantoprazole sodium capsules are prepared as enteric-coated capsules so that absorption of pantoprazole sodium begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole sodium does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole sodium declines biexponentially, with a terminal elimination half-life of approximately 1 hour.
In extensive metabolisers with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole sodium tablet, the peak concentration (C_{max}) is 2.5 mcg/mL; the time to reach the peak concentration (t_{max}) is 2.5 hours, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 mcgh/mL (range: 1.4–13.3 mcgh/mL). Following intravenous administration of pantoprazole sodium to extensive metabolisers, its total clearance is 7.6–14.0 L/hour, and its apparent volume of distribution is 11.0–23.6 L.

Absorption

Pantoprazole sodium is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 hours p.a., the maximum serum concentrations of about 2–3 mcg/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 10–80 mg, the plasma kinetics of pantoprazole sodium is 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 the AUC, maximum serum concentrations and, thus, bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

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

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). 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

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged 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 sodium is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole sodium, 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 sodium.

Patients with Renal Impairment

No dose reduction is recommended when pantoprazole sodium is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole sodium's half-life is short. Only very small amounts of pantoprazole sodium are dialysed. Although the main metabolite has a moderately delayed half-life (2–3 hours), excretion is still rapid and, thus, accumulation does not occur.

Patients with Hepatic Impairment

Although for patients with liver cirrhosis (Child-Pugh classes A and B), the half-life values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum serum concentration only increased slightly by a factor of 1.5, compared with healthy subjects.

Geriatric Patients

A slight increase in the AUC and C_{max} in elderly volunteers, compared with younger counterparts, is also not clinically relevant.

Paediatric Patients

Following administration of single oral doses of 20 mg or 40 mg pantoprazole sodium to children aged 5 to 16 years, the AUC and C_{max} were in the range of corresponding values in adults.
Following administration of single intravenous doses of 0.8 mg or 1.6 mg/kg pantoprazole sodium to children aged 2 to 16 years, there was no significant association between pantoprazole sodium clearance and age or weight. The AUC and volume of distribution were in accordance with data from adults.

Domperidone

Absorption

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 15–30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. 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 to induce its own metabolism; a peak plasma level of 21 ng/mL after 90 minutes (after 2 weeks of oral administration of 30 mg per day) was almost the same as that of 18 ng/mL after the first dose. Domperidone is 91–93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats

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 CYP450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31% and 66% of the oral dose, respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7–9 hours in healthy subjects but is prolonged in patients with severe renal impairment.

Special Populations

Hepatic Impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on C_{max} and AUC, with no change in protein-binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment.

Renal Impairment

In subjects with severe renal insufficiency (creatinine clearance <30 mL/min/1.73 m^2) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency.
However, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric Patients

No pharmacokinetic data are available in the paediatric population.

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

Pantoprazole
Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
In the 2-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 2-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 sodium'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 sodium-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 foetotoxicity 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 sodium in the foetus is increased shortly before birth.

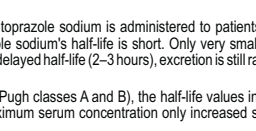
Domperidone

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- to 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison with the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered three times a day. Safety margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by 45-fold. Safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by 9-fold 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 torsades de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by more than 22-fold and 435-fold, respectively. In the anaesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered three times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.
In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold. 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.

7. DESCRIPTION

Pantoprazole

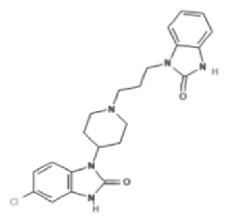
The active ingredient in pantoprazole sodium a PPI, is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C16H14F2N3NaO4S x 1.5 H2O, with a molecular weight of 432.4g/mol. The structural formula of pantoprazole is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

Domperidone

A specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms. Domperidone is chemically known as 6-chloro-3-[1-[3-(2-oxo-3*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1*H*-benzimidazol-2-one. It has a molecular formula of $C_{22}H_{24}ClN_5O_2$ and molecular weight of 425.9g/mol. The structural formula of domperidone is:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities: Not Applicable

8.2 Shelf-life

Please refer details on blister / carton

8.3 Packaging information

Alu-Alu blister of 10 capsules

8.4 Storage and handling instructions

Store protected from moisture, at a temperature not exceeding 25°C.

9. PATIENT COUNSELLING INFORMATION

What is Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules?

Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules contain the active substances, pantoprazole sodium and domperidone. Pantoprazole sodium is a selective proton-pump inhibitor (PPI), a medicine that reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.
Pantoprazole sodium is used to treat adults and adolescents, 12 years of age and above, for the following:
• Reflux oesophagitis, which is an inflammation of your oesophagus (the tube that connects your throat to your stomach) accompanied by the regurgitation of stomach acid.
• Pantoprazole sodium is used to treat adults with stomach and duodenal ulcers.
• Domperidone belongs to a group of medicines called 'dopamine antagonists' having anti emetic properties. It used in adults and in children to treat nausea (feeling sick) and vomiting (being sick).

Do not take if you have an allergy to this drug

This product should not be used by patients who are hypersensitive to any of the ingredients.

Before you take Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules, tell your HCP about other conditions you have and medications you may be taking:

If you have severe liver problems. Please tell your doctor if you ever had problems with your liver in the past because your liver enzymes need to be checked more frequently, especially when you are taking pantoprazole sodium as a long-term treatment. In the case of an increase in liver enzymes, the treatment should be stopped.
If you have reduced body stores or risk factors for reduced vitamin B_{12} and receive long- term treatment with pantoprazole sodium. As with all acid-reducing agents, pantoprazole sodium may lead to a reduced absorption of vitamin B_{12}.
If you are taking HIV protease inhibitors such as atazanavir (for the treatment of HIV-infection) at the same time as pantoprazole sodium, ask your doctor for specific advice.
Taking a PPI such as pantoprazole sodium, especially over a period of more than 1 year, may slightly increase your risk of fracture in the hip, wrist, or spine. Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis).
If you are on pantoprazole sodium for more than 3 months it is possible that the levels of magnesium in your blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, and increased heart rate. If you get any of these symptoms, please tell your doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium.
If you have ever had a skin reaction after treatment with a medicine similar to pantoprazole sodium that reduces stomach acid.
If you get a rash on your skin, especially in areas exposed to the sun, tell your doctor as soon as you can, as you may need to stop your treatment with pantoprazole sodium. Remember to also mention any other ill-effects such as pain in your joints.
If you are due to have a specific blood test (chromogranin A).
Tell your doctor immediately, before or after taking this medicine, if you notice any of the following symptoms, which could be a sign of another, more serious, disease:
• An unintentional loss of weight
• Vomiting, particularly if repeated
• Vomiting blood; this may appear as dark coffee grounds in your vomit
• You notice blood in your stools, which may be black or tarry in appearance
• Difficulty in swallowing or pain when swallowing
• You look pale and feel weak (anaemia)
• Chest pain
• Stomach pain
• Severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea You have a tumour of the pituitary gland (prolactinoma)
• You have a blockage or tear in your intestines
• You have black, tarry bowel motions (stools) or notice blood in your bowel motions. This could be a sign of bleeding in the stomach or intestines.
• You have a moderate or severe liver disease.
• Your ECG (electrocardiogram) shows a heart problem called 'prolonged QT corrected interval'.
• You have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure)
• You suffer from kidney problems (kidney function impairment or failure).
• You have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.
• You are taking certain medicines
If you are not sure, talk to your doctor or pharmacist before taking domperidone.
Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole sodium also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.
If you take pantoprazole sodium on a long-term basis (longer than 1 year), your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Children and adolescents

Pantoprazole sodium is not recommended for use in children as it has not been proven to work in children below 12 years of age.

Other medicines and pantoprazole sodium

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This is because pantoprazole sodium may influence the effectiveness of other medicines, so tell your doctor if you are taking the following:
• Medicines such as ketoconazole, itraconazole and posaconazole (used to treat fungal infections) or erlotinib (used for certain types of cancer) because pantoprazole aosium may stop these and other medicines from working properly.
• Warfarin and phenprocoumon, which affect the thickening, or thinning of the blood. You may need further checks.
• Medicines used to treat HIV-infection, such as atazanavir.
• Methotrexate (used to treat rheumatoid arthritis, psoriasis, and cancer) – if you are taking methotrexate, your doctor may temporarily stop your pantoprazole sodium treatment because pantoprazole sodium can increase levels of methotrexate in the blood.
• Fluvoxamine (used to treat depression and other psychiatric diseases) – if you are taking fluvoxamine your doctor may reduce the dose.
• Rifampicin (used to treat infections).
• St John's wort (Hypericum perforatum) (used to treat mild depression).

Pregnancy and breastfeeding

There are no adequate data from the use of pantoprazole sodium in pregnant women. Excretion into human milk has been reported.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.

Driving and using machines

Pantoprazole sodium has no or negligible influence on the ability to drive and use machines. If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

Other medicines and domperidone

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you can buy without a prescription, including herbal medicines. This is because domperidone can affect the way some other medicines work. Also, some medicines can affect the way domperidone works.
Do not take domperidone if you are taking medicine to treat the following:
• Fungal infections such as azole antifungals, specifically oral ketoconazole, fluconazole or voriconazole.
• Bacterial infections, specifically erythromycin, clarithromycin, telithromycin, moxifloxacin, pentamidine (these are antibiotics)
• Heart problems or high blood pressure (e.g. amiodarone, dronedarone, quinidine, disopyramide, dofetilide, sotalol, diltiazem, verapamil)
• Psychoses (e.g. haloperidol, pimozide, sertindole)
• Depression (e.g. citalopram, escitalopram)
• Gastro-intestinal disorders (e.g. cisapride, dolasetron, prucalopride)
• Allergy (e.g. mequitazine, mizolastine)
• Malaria (in particular halofantrine)
• AIDS/HIV (protease inhibitors)
• Cancer (e.g. toremifene, vandetanib, vincamine)
Tell your doctor or pharmacist if you are taking drugs to treat infection, heart problems or AIDS/HIV.

Domperidone and apomorphine

Before you use domperidone and apomorphine, your doctor will ensure that you tolerate both medicines when used simultaneously. Ask your doctor or specialist for a personalised advice.
It is important to ask your doctor or pharmacist if domperidone is safe for you when you are taking any other medicines, including medicines obtained without prescription.
It is recommended to take Domperidone before meals, as when taken after meals the absorption of the medicine is slightly delayed.

Pregnancy and breastfeeding

Talk to your doctor or pharmacist before taking domperidone if
• You are pregnant, might become pregnant or think you may be pregnant
• You are breastfeeding. It is best not to take domperidone if you are breastfeeding.
Small amounts of domperidone have been detected in breast milk. Domperidone may cause unwanted side effects affecting the heart in a breastfed baby. Domperidone should be used during breastfeeding only if your physician considers this clearly necessary. Ask your doctor for advice before taking this medicine.
Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day.
The risk also increases when domperidone is given together with some drugs. Tell your doctor or pharmacist if you are taking drugs to treat infection (fungal infections or bacterial infection) and/or if you have heart problems or AIDS/HIV.
Domperidone should be used at the lowest effective dose in adults and children.
While taking domperidone, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with domperidone should be stopped.

Driving and using machines

Domperidone does not affect your ability to drive or use machines.

How to take Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Method of administration

The recommended dose of Pantoprazole Gastro-Resistant & Domperidone Prolonged-Release Capsules is one capsule daily before breakfast.

What are the possible side effects?

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If you get any of the following side effects, stop taking these capsules and tell your doctor immediately, or contact the casualty department at your nearest hospital:

Pantoprazole

Serious allergic reactions (frequency rare; *may affect up to 1 in 1,000 people):* swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema/angio-oedema), severe dizziness with very fast heartbeat and heavy sweating.
Serious skin conditions (frequency not known; frequency cannot be estimated from the available data): blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of the eyes, nose, mouth/lips or genitals (Stevens-Johnson syndrome, Lyell syndrome, erythema multiforme), and sensitivity to light.
Other serious conditions (frequency not known: frequency cannot be estimated from the available data): acute kidney injury, yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination, and lower back pain (serious inflammation of the kidneys), possibly leading to kidney failure.

Other side effects

Common (may affect up to 1 in 10 people)
Benign polyps in the stomach.
Uncommon (may affect up to 1 in 100 people)
Headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders; fracture of the hip, wrist or spine.
Rare (may affect up to 1 in 1,000 people)
Distortion or complete lack of the sense of taste; disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; high fever; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
Very rare (may affect up to 1 in 10,000 people)
Disorientation
Not known (frequency cannot be estimated from the available data)
Hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood, decreased magnesium level in blood, feeling of tingling, prickling, pins and needles, burning sensation or numbness, rash, possibly with pain in the joints; inflammation in the large bowel, that causes persistent watery diarrhoea.

Side effects identified through blood tests

Uncommon (may affect up to 1 in 100 people): an increase in liver enzymes.
Rare (may affect up to 1 in 1,000 people): an increase in bilirubin; increased fat levels in blood; sharp drop in circulating granular white blood cells, associated with high fever.
Very rare (may affect up to 1 in 10,000 people): a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections; coexisting abnormal reduction in the number of red and white blood cells, as well as platelets.

Domperidone

Stop taking domperidone and see your doctor or go to a hospital straightaway in case of the following:
• You get swelling of the hands, feet, ankles, face, lips or throat which may cause difficulty in swallowing or breathing. You could also notice an itchy, lumpy rash (hives) or nettle rash (urticaria). This may mean you are having an allergic reaction to domperidone.
• You notice any uncontrolled movements. These include irregular eye movements, unusual movements of the tongue, and abnormal posture such as a twisted neck, trembling and muscle stiffness. This is more likely to happen in children. These symptoms should stop once you stop taking domperidone.
• You have a very fast or unusual heartbeat. This could be a sign of a life-threatening heart problem.
• You have a fit (seizure)

Other side effects

Common (affects less than 1 in 10 people)
• Dry mouth
Uncommon (affects less than 1 in 1,00 people)
• Lowering of sexual drive (libido) in men
• Feeling anxious
• Feeling drowsy
• Headaches
• Diarrhoea
• Itchy skin. You may also have a rash
• Unusual production of breast milk in men and women
• Painful or tender breasts
• A general feeling of weakness
Not known (Frequency cannot be estimated from the available data)
Disorders of the cardiovascular system: heart rhythm disorders (rapid or irregular heart beat) have been reported; if this happens, you should stop the treatment immediately. Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day.
• Domperidone should be used at the lowest
• effective dose in adults and children.
• Feeling agitated or irritable
• Feeling more nervous than usual
• Abnormal eye movements
• Inability to urinate
• Breast enlargement in men
• In women, menstrual periods may be irregular or stop
• A blood test shows changes in the way your liver is working.
Some patients who have used domperidone for conditions and dosages requiring longer term medical supervision have experienced the following unwanted effects: restlessness; swollen or enlarged breasts, unusual discharge from breasts, irregular menstrual periods in women, difficulty breastfeeding, depression, hypersensitivity. Side effects such as feeling drowsy, nervous, agitated or irritable or having a fit are more likely to happen in children.

10. Details of manufacturer

Windlas Biotech Limited (Plant-2),
Khasra No. 141 to 143 & 145, Mohabewala Indl. Area,
Dehradun-248110, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No.: 34/UA/2013 Dated: 03/09/2021

12. Date of revision

Not Applicable

Marketed by :

SEYNAPSIS
The Nexus of Health and Innovation

Seynapsis Pharma Pvt. Ltd.
Aakash Ganga Bldg-D, Flat No.-105
Rahatani Pimpri Colony, Pune,
Maharashtra-411017

Size : 232x555 mm Folded Size : 116x70 mm

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