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Product Name:	**CARDAL** (Enteric coated pantoprazole sodium and sustained release Domperidone capsules)

1.3 PRODUCT INFORMATION

1.3.1 Summary of Product characteristics (SmPC)

1. Name of the Medicinal Product:

1.1 Name of the Medicinal Product

- Brand Name / Generic Name: CARDL (Enteric coated pantoprazole sodium and sustained release Domperidone capsules)

- International Non-Proprietary Name (INN): Enteric coated pantoprazole sodium and sustained release Domperidone capsules

1.2 Strength: Pantoprazole sodium 40 mg & Domperidone 30 mg

1.3 Pharmaceutical Form: Hard gelatin capsule

2. Qualitative and Quantitative Composition :

Each hard gelatin capsule contains:
Pantoprazole sodium USP (As Sesquihydrate)
Eq.to Pantoprazole 40 mg
(As enteric coated pellets)
Domperidone BP 30 mg
(As sustained release pellets)
Excipients Q.S
Colour: Indigo carmine & Sunset yellow FCF

3. Pharmaceutical Form:

Pink cap and clear transparent body, size "2", hard gelatin capsule containing multi coloured spherical pellets.

4. Clinical Particulars

4.1 Therapeutic indications

- Gastro-oesophageal reflux disease (GERD)
- Erosive oesophagitis (EE)
- Gastric and duodenal ulcers
- The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal
- discomfort and regurgitation of gastric contents.

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4.2 Posology and method of administration

Posology

The recommended dose of CARDAL Capsules is one capsule daily before breakfast.

Method of administration

For oral use. Capsule should be swallowed whole with fluid.

4.3 Contraindications

Pantoprazole

Pantoprazole tablets 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 tablets, 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

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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 tablets. 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 tablets 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 tablets, 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 B12) 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.

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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 tablets.

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 Inhibtiors
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.

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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 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-prolonging 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 coadministration.

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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 Interaction with others medicinal products and other forms of 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.

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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)

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- 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).

4.6 Pregnancy and Lactation

Pregnant Women
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.

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

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

5. Pharmacological properties

5.1 Pharmacodynamics

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 doseresponse 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.

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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.

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 tablets, elevated gastrin levels return to normal by at least 3 months. 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.

5.2 Pharmacokinetics

Pantoprazole

Pantoprazole sodium capsule are prepared as hard gelatin capsule so that absorption of pantoprazole sodium begins only after the capsule leaves the stomach. Peak serum concentration (Cmax) 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.

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.

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Distribution

Pantoprazole's serum protein-binding is about 98%. Volume of distribution is about 0.15 l/kg.

Elimination

Pantoprazole sodium is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19, with subsequent sulphate conjugation; other metabolic pathways include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/hour/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole sodium to the proton pumps of the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole sodium; the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole sodium.

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

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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 Cmax 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.

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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 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 Cmax 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 m2) 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.

5.3 Preclinical safety data

Pantoprazole & Domperidone

Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

PHARMACEUTICALS PVT. LTD. **REGIONAL ADMINISTRATIVE INFORMATION**

CARDAL

Product Name: (Enteric coated pantoprazole sodium and sustained release Domperidone capsules)

5.Pharmaceutical particulars

6.1 List of excipients

- Dummy pellets

6.2 Incompatibilities

None.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in cool dry place below 30˚ C, Protect from light.

6.5 Nature and contents of container

3 X 10 Alu-Alu packing

6.Marketing Authorization holder

BEKRAPHARMA UKLTD.
13/091,L AVINGTON ROAD,
BEDDINGTON,
LONDON.
UNITED KINGDOM

8. Marketing Authorization Number

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9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text January 15th, 2019

CARDAL (Enteric coated pantoprazole sodium and sustained release Domperidone capsules)