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

Rabeprazole & Sustained Release Domperidone Capsules

ANTA™-DSR

अन्ता-डीएसआर

COMPOSITION :
Each hard gelatin capsule contains:

Rabeprazole Sodium IP (as enteric coated pellets)	20 mg
Domperidone IP (as sustained release pellets)	30 mg
Excipients	q.s.
Colours : Lake of Red Oxide of Iron & Lake of Sunset Yellow FCF Approved colours used in capsule shells.	

PHARMACEUTICAL FORM
Hard Gelatin Capsule.

THERAPEUTIC INDICATION
Indicated for the treatment of adult patients with gastroesophagal reflux disease (GERD).

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage is 1 capsule once daily or as directed by the Physician.
Method of administration: For oral use only.
This hard gelatin capsule should be swallowed whole with liquid and should not be chewed or crushed.

CONTRAINDICATIONS
Contraindicated in patients with a known hypersensitivity to the any of the active substance or to any excipients. Domperidone contraindicated in:
Prolactin-releasing pituitary tumour (prolactinoma).
When stimulation of the gastric motility could be harmful e.g in the patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation.
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, at the exception of apomorphine.
Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Rabeprazole
Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance. A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.
No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole is first initiated in such patients.
Treatment with proton pump inhibitors, including rabeprazole, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile.
Co-administration of atazanavir with rabeprazole is not recommended.
Paediatric population: Rabeprazole is not recommended for use in the children due to a lack of data on safety and efficacy. There have been post marketing reports of the blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole. Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.
Subacute cutaneous lupus erythematosus (SCLE): Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Rabeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.
Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
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), 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 for osteoporosis-related fractures should be managed according to the established treatment guidelines.
Interactions with Diagnostic Investigations for Neuroendocrine Tumors: 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 tumors. Providers should temporarily stop rabeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high.
Domperidone
Renal Impairment: The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.
Cardiovascular effects: Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.
Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patient with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.
Domperidone should be used at the lowest effective dose in adults and children.
Use with apomorphine: Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks.
Use in infants: Neurological side effects are rare (see "Undesirable effects" section). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

DRUG INTERACTION
Rabeprazole
Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur.
Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.
In clinical trials, antacids were used concomitantly with the administration of rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.
Co-administration of atazanavir 300 mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.
Domperidone
Concomitant administration of anticholinergic drugs may antagonize the anti-dyspeptic effect of domperidone.
The main metabolic pathway of domperidone is through CYP3A4. Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

USE IN SPECIAL POPULATION
Pregnancy
There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole 20mg enteric coated tablet is contraindicated during pregnancy.
There are limited post-marketing data on the use of domperidone in pregnant women. Domperidone is not recommended in pregnancy.
Breastfeeding
It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore Rabeprazole 20mg enteric coated tablet must not be used during breast feeding.
Studies have shown that domperidone enters breast milk. It is not known whether this is harmful to the newborn. Therefore, breast feeding is not recommended for mothers who are taking domperidone.
Paediatric population
Rabeprazole, not recommended for use in children due to a lack of data on safety and efficacy.
Due to the need for accurate dosing, Domperidone tablets are unsuitable for use in children and adolescents weighing less than 35 kg.
The safety and effectiveness of this product in pediatric patients has not been established.
Renal Impairment
The Capsules should be used with caution in patients with renal impairment or in those at risk of fluid retention. Patients on prolonged therapy should be reviewed regularly.
Hepatic Impairment
Since domperidone is highly metabolized in the liver, this Capsule should be not be used in patients with hepatic impairment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole 20mg enteric coated tablet would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.
Domperidone has no or negligible influence on the ability to drive or use machines.

UNDESIRABLE EFFECTS/ ADVERSE DRUG REACTIONS
Rabeprazole
Proton Pump Inhibitors associated Acute Kidney Injury : Acute kidney injury has been reported with the use of Proton pump inhibitors (PPIs) including Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole etc.
The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature. The following adverse events have been reported from clinical trial and post-marketed experience. Frequencies are defined as: 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), not known (cannot be estimated from the available data):
Common: Headache, Dizziness, Cough, Pharyngitis, Rhinitis, Diarrhoea, Vomiting, Nausea, Abdominal pain, Constipation, Flatulence, Fundic gland polyps (benign), Infection, Insomnia, Non-specific pain, Back pain, Asthenia, Influenza like illness.
Uncommon: Nervousness, Somnolence, Bronchitis, Sinusitis, Dyspepsia, Dry mouth, Eructation, Rash, Erythema, Myalgia, Leg cramps, Arthralgia, Fracture of the hip,wrist or spine, Urinary tract infection, Chest pain, Chills, Pyrexia, Increased hepatic enzymes.
Rare: Neutropenia, Leucopenia, Thrombocytopenia, Leucocytosis, Hypersensitivity, Anorexia, Depression, Visual disturbance, Gastritis, Stomatitis, Taste disturbance, Microscopic colitis, Hepatitis, Jaundice, Hepatic encephalopathy, Pruritus, Sweating, Bullous reactions, Interstitial nephritis, Weight increased.
Very Rare: Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS).
Not known: Confusion, Hyponatremia, Hypomagnesaemia, Peripheral oedema, Subacute cutaneous lupus erythematosus, Gynecomastia.
Domperidone
Immune system disorder: Very rare; Allergic reaction.
Endocrine disorder: Rare; increased prolactin levels.
Nervoussystem disorders: Very rare; extra pyramidalside effects.
GI disorders: Rare gastro-intestinal disorders including very rare transient intestinal cramps.
Skin and subcutaneous tissue disorders: Very rare; urticaria.
Reproductive system and breast disorders: Rare; galactorrhoea, gynaecomastia, amenorrhoea.
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.
Paediatric population: Extrapyramidal disorder occurs primarily in neonates and infants.
Other central nervous system-related effects of convulsionand agitation alsoare primarily reported in infants and children.

OVERDOSE
Rabeprazole
Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.
Domperidone
Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, disorientation, somnolence and extrapyramidal reactions. There is no specific antidote to domperidone; but in the event of overdose, gastric lavage as well as the administration of activated charcoal may be useful. Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Drugs for acid-related disorders, Proton pump inhibitor, and Dopamine antagonist.
Rabeprazole, is a selective and irreversible proton pump inhibitor, suppresses gastric acid secretion by specific inhibition of the H+, K+ -ATPase, which is found at the secretory surface of parietal cells. In doing so, it inhibits the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen. Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.
Domperidone, is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extra-pyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in humans have shown oral domperidone to increase lower esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

PHARMACOKINETIC PROPERTIES
Absorption
Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52 % due in large part to pre-systemic metabolism.
In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone`s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastrointestinal complaints should take domperidone 15 to 30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone.
Distribution
Rabeprazole is approximately 97 % bound to human plasma proteins.
Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21ng/ml 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% to 93% bound to plasma proteins.
Metabolism
Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).
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
Following a single 20 mg 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90 % of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.
Urinary and fecal excretions amount to 31% and 66% of the oral domperidone dose, respectively. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects, but is prolonged in patients with severe renal impairment.

INCOMPATIBILITY
Not applicable.

STORAGE INSTRUCTIONS
Store protected from light & moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.
Capsule should be swallowed whole and not to be opened, chewed or crushed.

Manufactured by :
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