

RAYZOLE – D CAPSULE

Composition :

Each enteric coated tablet contains :

Rabeprazole Sodium I.P. 20mg.

Domperidone I.P. 30mg.

(As sustained release pellets)

DESCRIPTION :

RABEPRAZOLE

Rabeprazole belong to the class of Proton Pump Inhibitor. It is used to prevent and heal gastro-intestinal problems which are caused due to hyperacidity in the stomach. Sometimes this drug is identified as an ulcer healing drug. This is also very beneficial for inhibiting gastric acid secretion. It heals stomach and intestinal ulcers and manages Gastro-Oesophageal Reflux Disease.

DOMPERIDONE

Domperidone is a dopamine antagonist with anti-emetic properties, it does not readily cross the blood brain barrier. Its anti-emetic effect may be due to a combination of gastrokinetic and antagonism to dopamine receptors in the chemo receptor triggered zone, which lies outside the blood brain barrier in the area postrema. Domperidone to increase Lower Esophageal Pressure (LEP), improve antro-duodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

MECHANISM OF ACTION :

Pharmacodynamic

RABEPRAZOLE

Rabeprazole is partially reversible inhibitor of Proton Pump which is activated in the acidic lumen of the gastric parietal cell. The canalicular membrane of the gastric parietal cells contains the Proton Pump ($H^+K^+ATPase$) enzyme. It exchanges H^+ ion for K^+ ion using energy generated by the breakdown of ATP to ADP. This enzyme represents the final step for acid production in the stomach.

DOMPERIDONE

Domperidone, a prokinetic agent act on the gastrointestinal activity by acting as a competitive at Dopamine D2 receptors. Dopamine inhibits gastrointestinal motility, reduces gastric and esophageal sphincter tone and inhibits gastro duodenal coordination. This effect of dopamine is inhibited by domperidone effectively as it increases esophageal peristalsis and lower esophageal sphincter pressure (LESP), increases gastric motility and peristalsis, enhances gastro duodenal coordination and consequently facilitates gastric emptying and decrease small bowel transit time. It is also known to act on the chemoreceptor trigger zone, producing an antiemetic activity.

Pharmacokinetics :

RABEPRAZOLE

Absorption : Absolute bioavailability for a 20 mg oral tablet of Rabeprazole (compared with intravenous administration) is approximately 52%. When it is administered with a high fat meal, T_{max} is variable; which

concomitant food intake may delay the absorption up to 4 hours or longer. However, the C_{max} and area under the curve (AUC) are not significantly altered. Thus, Rabeprazole sodium tablets may be taken without regard to timing of meals.

Distribution : Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism : Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. In vitro studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole.

Bioavailability : After oral administration of Rabeprazole-20mg., absolute bio availability was approximately 52% .

Excretion: Approximately 90% of the drug was eliminated in urine, primarily as thioether carboxylic acid, its glucuronide and mercapturic acid metabolites. The remainder unchanged 10% of the dose is recovered in the faeces.

DOMPERIDONE

Absorption : In fasting subjects, domperidone is rapidly absorbed after oral administration with peak plasma concentrations at 30-60 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 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 the oral drug is taken after a meal.

Distribution : Peak plasma level after 90 minutes of 21ng/mL after two weeks oral administration of 30mg. per day was almost the same that of 18ng/mL after the first dose. Domperidone is 91-93 % bind to plasma protein. It does not rapidly cross the blood barrier and therefore is not expected to have central effects. However, according to animal studies, very low amount cross the placental barrier and it is excreted in the breast milk.

Metabolism : Oral domperidone does not appear to accumulate or induce its own metabolism . It 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 CYP-450 involved in the N-dealkylation, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion : Domperidone is excreted through both urinary and faecal routes. Approximately 30% through urine and 66% through faecal. It is excreted as unchanged drug in a very small quantity (approximately 10% through faecal and 1% through urine). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects, but is prolonged in patients with severe renal insufficiency.

RATIONAL FOR COMBINATION :

As Rabeprazole is the fastest acting Proton Pump Inhibitor so, it gives a quicker relief from the hyper acid secretion condition. A significant percentage of GERD patients have delayed gastric emptying rate and hypotensive esophageal sphincter. Domperidone is a prokinetic drug that improves the LES tone, increases the gastric motility and thus help in faster gastric emptying. In GERD patients not responding to Rabeprazole alone, combination of Rabeprazole and Domperidone may be effective.

INDICATIONS :

This combination (Rayzole-D) can be used in GERD, Dyspepsia, Chronic Gastritis, Erosive Esophagitis, Post-operative Nausea and Vomiting, and Nausea associated with Acid Peptic Disorders.

DOSAGE AND ADMINISTRATION :

One capsule once daily.

DRUG INTERACTION :

RABEPRAZOLE :

pH dependent interactions with digoxin and ketoconazole .

DOMPERIDONE :

- (a) Concomitant administration of anticholinergic drugs may decrease the effect of domperidone.
- (b) An azole antifungals/macrolides antibiotic increases plasma level of domperidone.

SIDE EFFECT :

Generally well tolerated. Most common side effects are headache, dizziness, abdominal pain, diarrhea, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia and arthralgia, dry mouth and blurring of vision. Many people using this medication do not have serious side effects.

CONTRAINDICATIONS :

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

Domperidone is contraindicated to the patients with known hypersensitivity to domperidone or any of the excipients.

Domperidone should not be used in the condition like gastrointestinal haemorrhage, mechanical obstruction or perforation.

PRECAUTIONS :

Patient should not take Rabeprazole if they have allergic problem to it or to other PPI or have any other allergies.

This product may contain inactive ingredients, which can cause allergic reactions or other problems. So, before taking Rabeprazole patient must consult to the doctor.

Before using this medication, patient should consult to the doctor or pharmacist regarding other medical history, especially of liver disease.

Some symptoms may actually be signs of a more serious condition. Get medical help right away if patients have heartburn with light headedness, sweating, dizziness. Proton pump inhibitors (such as rabeprazole) may increase the risk for bone fractures, especially with longer use, higher doses, and in older adults.

Lactation : It is unknown if this medication passes into breast milk. However, similar drugs pass into breast milk. The effects on a nursing infant are unknown.

Renal Impairment : Rayzole- D Capsules should be used with caution in patients with renal impairment or in those at risk of fluid retention. In patients with severe renal impairment (serum creatinine more than 6 mg/100 ml i.e..more than 0.6mmol/L),the elimination half-life of domperidone was increased. The dosing frequency should be altered, depending on the severity of impairment and the dose may need to be reduced. Patients on prolonged therapy should be reviewed regularly.

Hepatic Impairment : Since domperidone is highly metabolized in the liver, so Rayzole-D Capsules should not be used in patients with hepatic impairment.

Pregnancy : There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation : It is unknown if this medication passes into breast milk. However, similar drugs pass into breast milk. The effects on a nursing infant are unknown. Consult your doctor before breast-feeding.

Paediatric Use : The safety and effectiveness of this product in paediatric patients has not been established.

OVERDOSE :

RABEPRAZOLE : There has been no experience with large overdoses with rabeprazole. Rabeprazole is extensively protein-bound and is not readily dialysable. In the event of overdose, treatment should be symptomatic and supportive. The major symptoms of acute toxicity Rabeprazole were hypoactivity, laboured respiration, lateral or prone position and convulsion in mice and rats and watery diarrhoea, tremor, convulsion and coma in dogs.

DOMPERIDONE : Overdose has been reported primarily in infants and children. Symptoms of overdose 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.

STORAGE :

Store in a dark and dry place. Protect from light, 15-30 Degree Celsius.

PACKING INFORMATION :

Rayzole- D Capsules are presented in a Alu-Alu strip of 10 capsules.