COMPOSITION :

Each capsule contains

Rabeprazole sodium IP		
Equivalent to Rabeprazole (As enteric coated pellets)	……..	20 mg
Domperidone (As sustained release pellets)	……..	q.s

DESCRIPTION :

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2 -receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+/K + ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide.

Domperidone is a derivative of benzimidazole that possesses both prokinetic and antiemetic properties due to its inhibitory action at dopamine D2 receptors.

PHARMACOLOGY :

Pharmacodynamics:
Mechanism of Action
Rabeprazole

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide.

When studied in vitro, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

Antisecretory Activity
The antisecretory effect begins within one hour after oral administration of 20 mg rabeprazole. The median inhibitory effect of rabeprazole on 24 hour gastric acidity is 88% of maximal after the first dose. Rabeprazole 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table below). This relatively prolonged Pharmacodynamics action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H+, K+ ATPase.

Domperidone

Domperidone is a dopamine antagonist with anti-emetic properties domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal 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 man have shown oral domperidone to increase lower esophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Pharmacokinetics:

Rabeprazole

After oral administration of 20 mg rabeprazole, peak plasma concentrations (Cmax) of rabeprazole occur over a range of 2.0 to 5.0 hours (Tmax). The rabeprazole C max and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Absorption

Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. Rabeprazole may be taken without regard to timing of meals.

Distribution

Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism

Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. 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.The thioether metabolite is formed non-enzymatically by reduction of rabeprazole.

Excretion

Following a single 20 mg oral dose of 14 C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. No unchanged rabeprazole was recovered in the urine or feces.

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 gastro-intestinal 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 :

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks 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 cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and fecal excretions amount to 31 and 66% of the oral 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 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

INDICATIONS :

RAZOCER-DSR is indicated for the relief of symptoms of
1. Dyspepsia.
2. GERD.
3. Nausea associated with acid peptic disorders.
4. Post-operative nausea and vomiting.
5. Chronic gastritis.

DOSAGE AND ADMINISTRATION :

One capsule a day or as directed by the physician.

CONTRAINDICATIONS :

RAZOCER-DSR is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazole, Domperidone or to any component of the formulation. It should not be used whenever stimulation of gastric motility is to be avoided or could be harmful, e.g. in the presence of gastro-intestinal hemorrhage, obstruction or perforation. It is also contra-indicated in patients with a prolactin-releasing pituitary tumor (prolactinoma).

ADVERSE EFFECTS :

Adverse effects with rabeprazole are mild to moderate in intensity and included malaise, diarrhea, nausea, skin eruptions, headache and dizziness. Abnormal laboratory findings (increased hepatic enzymes, LDH, blood urea nitrogen) observed with rabeprazole were similar in incidence and severity with comparator agents and reversible with cessation of therapy.

Domperidone has been found to be associated with increased serum prolactin, which may be associated with galactorrhea, less frequently gynaecomastia, breast enlargement and soreness. Reduced libido has been reported. Occasional rashes and other allergenic phenomena are also reported. Domperidone does not readily cross the normally functioning blood brain barrier and is therefore less likely to interfere with the central

dopaminergic function. However, acute extrapyramidal dystonic reactions have been reported with domperidone.

SHELF-LIFE :

2 years.

PACKAGING INFORMATION :

RAZOCER- DSR is available in an Alu - Alu pack of 10 capsules.