GASOSIQ-D

Each tablet contains Pantoprazole 40 mg and Domperidone 10 mg

Dosage Form and Strength

Dosage Form: Tablet.
Dosage Strength: Pantoprazole 40 mg with Domperidone 10 mg per tablet.

Clinical Particulars

Therapeutic Indication

GASOSIQ-D tablet are indicated for the treatment gastro-esophageal reflux disease (GERD) not responding adequately to pantoprazole alone.

Posology and Method of Administration

For oral administration in adults:

Recommended dose is 1 tablet to be administered once daily for 4 to 8 weeks.
GASOSIQ-D tablet may be administered with or without food. The tablet should be swallowed whole with water and not to be opened, chewed or crushed.
Or, as prescribed by the physician.

Pharmacological Properties

Mechanism of Action

Pantoprazole

Pantoprazole is a proton pump inhibitor (PPI) class of antisecretory agent. Pantoprazole is a lipophilic weak base that crosses the parietal cell membrane and enters the acidic parietal cell canaliculus where it becomes protonated, producing the active metabolite sulfenamide. Sulfenamide forms an irreversible covalent bond with two sites of the H+/K+-ATPase enzyme located on the gastric parietal cell. Thus, pantoprazole suppress the final step in gastric acid (hydrochloric acid – HCl) production by covalently binding to the H+/K+- ATPase enzyme (also called as proton pump) 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 duration of antisecretory effect that persists longer than 24 hours.

Domperidone

Domperidone is a dopamine receptor (D2) antagonist. Domperidone act predominantly on peripheral dopamine receptors and produces anti-emetic and gastrokinetic effects. Domperidone does not readily cross the blood-brain barrier (BBB). Thus, in domperidone users, especially in adults, extrapyramidal side effects are very rare (unlike metoclopramide). Anti-emetic effect of domperidone is due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors (D2) in the

chemoreceptor trigger zone (CTZ), which lies outside the BBB in the area postrema.

Oral domperidone also increases lower esophageal sphincter (LES) pressure, thus, improve antroduodenal motility and accelerate gastric emptying.

Pharmacodynamic Properties

Pantoprazole

With a single oral dose of 20 to 80 mg of pantoprazole, a dose-dependent decrease in gastric acid secretion occurs. Following the initial oral dose of 40 mg pantoprazole, 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%. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

Pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, and gastrin).

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases.

Domperidone

Prokinetic Effect: The prokinetic (gastrokinetic) properties of domperidone are related to its peripheral dopamine receptor blocking action.

Antiemetic Effect: Domperidone produces antiemetic effect by blocking dopamine receptors (D2) peripherally. Inhibition of peripheral D2 receptor signaling prevents or relieves various GI symptoms, such as nausea and vomiting, and also relieves reflux and other symptoms associated with upper GI disorders.

Pharmacokinetic Properties

Pantoprazole

Absorption: Like other PPIs, pantoprazole is an acid-labile drug and therefore, administered orally in the form of gastro-resistant pellets. Absorption of pantoprazole, therefore, begins in the intestine only after the pellets leave the stomach.

After administration of a single or multiple oral doses of pantoprazole 40 mg, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C_{max} was 2.5 mcg/ml. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increases in a dose-dependent manner (with dose range from 10 to 80 mg). Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%.

Effect of Antacid / Food: Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

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

Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. 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: Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole, the rest is excreted with the faeces. There is no renal excretion of unchanged pantoprazole. The main metabolite in both the serum and urine is desmethyl- pantoprazole which is conjugated with sulphate. Following oral administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

Domperidone

Pharmacokinetics of domperidone in prolonged-release formulation is not available. Conventional formulation of domperidone (i.e., immediate release) has following pharmacokinetic properties:

Absorption: Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hour after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first- pass metabolism in the gut and liver.

Effect of Food: Domperidone bioavailability is enhanced in normal subjects when taken after a meal. 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 induce its own metabolism. The peak plasma concentration (C_{max}) of 18 ng/ml to 21 ng/ml occurs 1.5 hours (T_{max}) after the oral dose. Domperidone is 91 to 93% bound to plasma proteins. Distribution studies with domperidone have shown wide tissue distribution, but low brain concentration.

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: After oral dose, domperidone is excreted mainly by renal (31%) and biliary (66%) routes. 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 insufficiency.