Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT: ITORAB-SR

(Enteric Coated Rabeprazole Sodium and Itopride Hydrochloride SR Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard gelatin Capsule Contains:
Rabeprazole Sodium BP 20mg
(As enteric coated pellets)
Itopride Hydrochloride 150mg
(As substained release pellets)
Excipients…….q.s
Approved colour used in capsules shell and pellets.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This combination medication contains a proton pump inhibitor and prokinetic agent, prescribed for gastro-esophageal reflux disease and peptic ulcer disease.

4.2 Posology and method of administration

Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Rabeprazole and Itopride Hydrochloride Tablets is to be taken empty stomach.

4.3 Contraindications

Alcohol: Caution is advised when consuming alcohol with Rabeprazole and Itopride Hydrochloride Tablets. Please consult your doctor.

Pregnancy: Rabeprazole and Itopride Hydrochloride Tablets may be unsafe to use during pregnancy. Although there are limited studies in humans, animal studies have shown harmful effects on the developing baby. Your doctor will weigh the benefits and any potential risks before prescribing it to you. Please consult your doctor.

Breastfeeding: CONSULT YOUR DOCTOR Information regarding the use of Rabeprazole and Itopride Hydrochloride Tablets using breastfeeding is not available. Please consult your doctor.

Driving: Rabeprazole and Itopride Hydrochloride Tablets may decrease alertness, affect your vision or make you feel sleepy and dizzy. Do not drive if these symptoms occur.

Kidney: There is limited information available on the use of Rabeprazole and Itopride Hydrochloride Tablets in patients with kidney disease. Please consult your doctor.

Liver: Rabeprazole and Itopride Hydrochloride Tablets should be used with caution in patients with severe liver disease. Dose adjustment of Rabeprazole and Itopride Hydrochloride Tablets may be needed. Please consult your doctor.

4.4 Special warnings and precautions for use

Symptomatic response to rabeprazole does not preclude the presence of gastric malignancy. Atrophic

gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with benzimidazoles to which group rabeprazole also belongs.
Rabeprazole, like other proton pump inhibitors, has potential to cause gastric carcinoids but the studies have not been conclusive. Rabeprazole Sodium & Itopride Hydrochloride tablets must not be opened, chewed or crushed; they should be swallowed as whole.

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole: Rabeprazole is metabolized in the liver by cytochrome P450 (CYP450). Hence, coadministration with warfarin could lead to increase in prothrombin time although it is not significant. Even metabolism of cyclosporine is inhibited by rabeprazole when concomitantly advocated. Since Rabeprazole Sodium & Itopride Hydrochloride inhibits gastric acid secretion, it could interfere with absorption of drugs wherein gastric pH is an important determinant of bioavailability like ketoconazole.
Itopride: No interactions with regard to serum binding have been detected for itopride with warfarin, diazepam, diclofenac, ticlopidine, nifedipine and vice-versa. Metabolic interactions are not to be expected because itopride is mainly metabolized by flavin monooxygenase and not by cytochrome P450. Anticholinergic agents may reduce the action of itopride. Antiulcer agents like cimetidine, ranitidine did not affect the prokinetic action of itopride.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy: Rabeprazole: Pregnancy Category B: 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.
Itopride: The safety of this product in pregnant women has not been established. Therefore, this product should only be used in pregnant women or women suspected of being pregnant, provided that the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment. No teratogenic effects have been detected in animals.
Use in Lactation: Rabeprazole: Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Itopride: Itopride hydrochloride is excreted with the breast milk in lactating rats. Treatment with Itopride should be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines:

NA

4.8 Overdose

Rabeprazole: There has been no experience with large overdoses with Rabeprazole. The maximum reported overdose was 80 mg. There was no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.
Itopride: There have as yet been no reports of overdose in humans. The oral single dose LD 50 was >2000 mg/kg in mice and rats and about 600 mg/kg in dogs. In case of excessive overdosage the usual measures of gastric lavage and symptomatic therapy should be applied. Itopride does not cause QT prolongation.

Summary of Product Characteristics

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamics: *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%. This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H^+, K^+ATPase.

Effects on Esophageal Acid Exposure: In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, Rabeprazole 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure.

Effects on Serum Gastrin: In patients given daily doses of rabeprazole for up to eight weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

Effects on Enterochromaffin-like (ECL) Cells: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females.

Endocrine Effects: Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system.

Other Effects: In humans treated with rabeprazole for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory

Itopride: ltopride promotes gastrointestinal motility through synergism of its dopamine D 2-receptor antagonistic action and its acetylcholine esterase inhibitory action. In addition to these actions, Itopride has an antiemetic action, which is based on its dopamine D2 receptor antagonistic action at CTZ.

5.2 Pharmacokinetic properties

Rabeprazole: Rabeprazole Sodium & Itopride Hydrochloride tablets are enteric coated to allow Rabeprazole sodium, which is acid labile to pass through the stomach relatively. 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 Cmax 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.
Itopride: Absorption: On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing. Food does not affect its absorption.
Metabolism: Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme
flavin-containing monooxygenase (FMO). Biotransformation of itopride does not involve the cytochrome P450 enzyme system, thus, it is devoid of drug interaction potential with cytochrome P450 enzyme inhibitors.
Excretion: The half-life of Itopride is about 6 hours. It is excreted mainly by the kidneys as metabolites and unchanged drug. Food did not significantly affect the absorption of Itopride.

5.3 Preclinical safety data

NA

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SR. NO.	INGREDIENTS	SPECIFICATION
1	Microcrystalline Cellulose	BP
2	Lactose	BP
3	HPMC	BP
4	Citric acid	BP
5	Povidone 30	BP
6	Purified water	BP
7	Magnesium Stearate	BP
8	Purified Talc	BP
9	Ferric Oxide	IH

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacturing.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 tablets are packed in one Alu-Alu blister such blister are packed in a carton with insert.

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

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