Summary of Product Characteristics for Pharmaceutical Products

1. Name of the pharmaceutical product:

SABEZOLE IT®

Enteric Coated Rabeprazole Sodium 20 mg and Sustained Release Itopride Hydrochloride 150 mg Capsules

2. Qualitative and Quantitative composition

Each hard gelatin capsule contains:
Rabeprazole Sodium BP.....20 mg
(As enteric coated pellets)
Itopride hydrochloride.....150mg
(As sustained release pellets)
Excipients.....q.s.
(for the full list of excipients, see section 6.1)

3. Pharmaceutical form:

Sustained Release Capsules.
Red/transperent coloured size "0" hard gelatine capsule shells Brick red and off white coloured pellets.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Gastroesophageal reflux disease, Gastric ulcers, Peptic ulcer, Zollingerellison syndrome, Stomach fullness and other conditions. It can be used in combination with appropriate antibacterial regimen for eradication of H.Pylori infection.

4.2 Posology and method of administration

Posology:

Usual Recommended Dose: One capsule to be taken once daily.

Method of administration:

SABEZOLE® IT should be swallowed whole and taken at least 1 hr before eating.

4.3 Contraindications

SABEZOLE® IT is contraindicated in patients with known hypersensitivity to Rabeprazole Sodium or itopride hydrochloride or any of the excipients.
Itopride hydrochloride should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g. gastrointestinal hemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or esophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole sodium.

A risk of cross-hypersensitivity reactions with substituted benzimidazoles cannot be excluded.
Severe hypomagnesaemia has been reported in patients treated with PPIs like rabeprazole for at least three months, and in most cases for a year. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
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 sodium. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Rabeprazole sodium treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Itopride hydrochloride enhances the action of acetylcholine and may produce cholinergic side effects.
In general, appropriate caution should be exercised in the administration and monitoring of Itopride hydrochloride in elderly patients reflecting the greater frequency of decreased hepatic, renal function, and of concomitant disease or other drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole sodium

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 sodium.

Co-administration of atazanavir 300 mg/ritonavir 100 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. Methotrexate case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Itopride Hydrochloride
Metabolic interactions are not expected since Itopride is primarily metabolized by flavine monooxygenase and not by CYP450.
No changes in protein binding have been seen with coadministration of warfarin, diazepam, diclofenac sodium, ticlopidine hydrochloride, nifedipine, and nicardipine hydrochloride.
Since itopride has gastrokinetic effects it could influence the absorption of concomitantly orally administered drugs. Particular caution should be taken with drugs with a narrow therapeutic index, sustained release or enteric-coated formulations.
Anti-ulcer drugs like cimetidine, ranitidine, teprenone and cetraxate do not affect the prokinetic action of itopride.
Anticholinergic drugs may reduce the action of itopride.

4.6 Pregnancy and lactation
Pregnancy
There are no data on the safety of rabeprazole in human pregnancy. SABEZOLE® IT is contraindicated during pregnancy.
Lactation
It is unknown whether rabeprazole sodium is excreted in human breast milk. No studies in breast-feeding women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore, SABEZOLE® IT should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines.
Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that SABEZOLE® IT would cause an impairment of driving performance or compromise the ability to use machinery. If, however, alertness is impaired due to somnolence or dizziness it is recommended that driving and operating complex machinery be avoided. Care should be taken before driving or using machinery until the patient's individual reaction on the medicine has been established.

4.8 Undesirable effects

Blood and lymphatic system disorders
Leukopenia, neutropenia and thrombocytopenia.

Immune system disorders
Hypersensitivity, Anaphylactoid reaction.

Endocrine disorders
Increased prolactin level and gynecomastia.

Nervous system disorders
Dizziness, headache, and tremor.

Gastrointestinal disorders
Diarrhoea, constipation, abdominal pain, increased saliva, and nausea.

Hepato-biliary disorders
Jaundice.

Skin and subcutaneous tissue disorders
Rash, redness, and itching.

Investigations
Increased AST (SGOT), increased ALT (SGPT), increased gamma-GTP, increased alkaline phosphatase, and increased bilirubin.

Other adverse events were rhinitis, asthenia, flatulence, pharyngitis, vomiting, non-specific pain/back pain, dizziness, flu syndrome, infection, cough, constipation and insomnia.
Further less frequent adverse events were myalgia, chest pain, dyspepsia, nervousness, somnolence, bronchitis, sinusitis, chills, leg cramps, urinary tract infection, arthralgia and fever.
In isolated cases, anorexia, gastritis, weight gain, depression, pruritus, vision or taste disturbances, stomatitis, sweating and leucocytosis have been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 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.
Itopride - There have been no reported cases of overdose in humans. In case of excessive overdose, the usual measures of gastric lavage and symptomatic therapy should be applied.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Rabeprazole, Combinations
ATC code: A02BC54

Rabeprazole sodium belongs to the class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+- ATPase enzyme at the secretory surface of the gastric parietal cell. This enzyme system is regarded as the acid (proton) pump, and therefore rabeprazole sodium is classified as a gastric proton-pump inhibitor blocking the final step of acid production. This 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 the weak base is rapidly absorbed and converted into sulphonamide (active form).

Anti-secretory Activity: After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. This duration of pharmacodynamic action is much longer than the pharmacokinetic halflife (approximately one hour) would predict. This effect is probably due to the prolonged binding to the parietal H+/K+- ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Serum Gastrin Effects: In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 24 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.
Itopride activates the gastrointestinal propulsive motility by dopamine D2 receptors antagonistic action and acetylcholinesterase inhibitory action.

Itopride activates acetylcholine release and inhibits its degradation. In addition, itopride has an antiemetic action which is based on interaction with

dopamine D2 receptors in chemoreceptor zone. Itopride accelerates stomach emptying in humans. Itopride has high specific action in upper part of gastrointestinal tract. Itopride does not influence plasma concentrations of gastrin.

5.2 Pharmacokinetic properties

Rabeprazole sodium

Absorption: Rabeprazole sodium is acid-labile, and is therefore administered orally as an enteric-coated (gastro-resistant) formulation. Absorption of rabeprazole sodium therefore begins only after the capsule leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole sodium 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. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma halflife is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 + 98 mL/min.

Distribution: Rabeprazole is approximately 97% bound to human plasma proteins.

Biotransformation and elimination: 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 humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma. 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.

Itopride

Absorption: Itopride is absorbed rapidly and almost completely from gastrointestinal tract. Relative bioavailability about 60% is due to first-pass effect. Food does not affect bioavailability of the product. Maximum plasma concentrations are reached in 30 to 50 minutes after administration of 50 mg of itopride. After repeated administration of doses in the range of 50 to 200 mg 3 times a day for period of 7 days, itopride and its metabolites have shown pharmacokinetics of linear type with minimal accumulation.

Distribution: About 96% of itopride is bound on plasma proteins, mainly albumin. Less than 15% of itopride bound part is bound on alpha-1-acid-glycoprotein. In rats, itopride is distributed extensively in the tissues (Vdß = 6.1 l/kg) except for central nervous system; high concentrations are reached in kidneys, small intestine, liver, adrenal glands and stomach. Protein binding in rats was lower than in humans (78% contrary to 96%). Penetration into the central nervous system was minimal. Itopride is excreted in milk of lactating rats.

Metabolism: Itopride undergoes extensive hepatic metabolism in humans. Three (3) metabolites have been identified, of which only one exerts minor activity without pharmacological relevance (approximately 2-3% of that of itopride). The primary metabolite in humans is the N-oxide, generated by oxidation of the tertiary amine N-dimethyl group. Itopride is metabolized by a flavin-dependent mono-oxygenase (FMO3). The abundance and efficiency of the human FMO-isozymes can be subject to genetic polymorphisms, which can lead to a rare autosomal recessive condition known as trimethylaminuria (fish odour syndrome). The half-life of itopride may therefore, be longer in trimethylaminuria patients. In vivo pharmacokinetic studies on CYP-mediated reactions revealed that itopride showed neither inhibitory nor inductory effect on CYP2C19 and CYP2E1. CYP content and uridine diphosphate glucuronosyl transferase activity were not altered with the administration of itopride.
Excretion: Itopride hydrochloride and its metabolites are primarily excreted in the urine. The urinary excretions of itopride and its N-oxide were 3.7% and 75.4%, respectively, in healthy subjects after oral administration of a single therapeutic dose.

5.3 Preclinical safety data
Rabeprazole sodium
Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

Itopride
Oral single lethal dose was 2,000 mg/kg in mice and rats and approximately 600 mg/kg in dogs. Preclinical safety studies were carried out only with doses multiplicatively overrunning therapeutic human doses and found effect have only little importance for use of itopride in humans. In addition to it humans are less sensitive to hormonal effects observed in animals.
High doses of itopride (30 mg/kg/day) caused hyperprolactinaemia and secondary reversible hyperplasia of uterine mucosa in rats. Nevertheless, this was not proved in dogs (dose up to 100 mg/kg/day) and monkeys (dose up to 300 mg/kg/day).

3-month toxicity study in dogs has revealed prostate atrophy after oral administration in dose 30 mg/kg/day. This effect was induced neither after 6-month administration of higher doses (100 mg/kg/day) in rats nor more higher doses (300 mg/kg/day) in monkeys.
Long-term studies of carcinogenicity in animals have not been carried out.
In series of in vitro and in vivo tests no clastogenic and mutagenic effects of itopride were found.
In fertility studies in female rats who were administered doses 30 mg/kg/day and higher, hyperprolactinaemia and secondary prolongation of oestral cycle were observed. Prolonged precoital interval was observed at doses 300 mg/kg/day.

6. Pharmaceutical particulars
6.1 List of Excipients:
Hard Gelatin capsule shell

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Store below 30°C, protect from direct sunlight, heat & moisture.

6.5 Nature and contents of container
SABEZOLE® IT is available in the pack of 1 x 10 Capsules.

6.6 Special precautions for disposal and other handling
Any unused medicine product or waste material should be disposed of in accordance with the local requirements.

7. Marketing authorization holder and manufacturing site addresses
Manufactured in India by:
Curis Lifesciences Ltd.
PF No-23, GIDC Industrial Estate,
Sanand-II, Ahmedabad-382110, Gujarat, India.

Manufactured For & Marketed by:
KRISHNA CHEMISTS LTD.
P.O. BOX 3328-00506
NAIROBI, KENYA.

8. Marketing authorisation number(s)
H2021/CTD5536/1797ER

9. Date of first Registration/ Renewal of Registration
Date of first authorization: 26th May 2020

10. Date of revision of text
25/04/2025