SUMMARY PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

ESOXIUM IT (Enteric Coated Esomeprazole Magnesium and Sustained Release Itopride Hydrochloride Capsules)

2. Quality and Quantitative Composition

Each capsule contains:
Esomeprazole Magnesium Trihydrate BP
equivalent to Esomeprazole : 40 mg
(as Esomeprazole pellets)
Itopride Hydrochloride : 150 mg
(as sustained release pellets)
Colour: Titanium Dioxide
Approved colours used in capsule shell.

For Excipients see section 6.1

3. Pharmaceutical Form:

Enteric Coated Capsule

'0' Size Hard Gelatin Capsules with Brown colour cap and Brown colour body containing off white coloured pellets.

4. Clinical Particulars

4.1 Therapeutic indications:

Treatment of GERD when esomeprazole monotherapy is inadequate.

4.2 Posology and methods of administration:

Usual Recommended Dose: 1 Capsule once daily.

Administration: Capsules should be swallowed whole and taken at least 1 hr before eating.

4.3 Contraindications

Hypersensitivity to esomeprazole, to other substituted benzimidazoles or to any of the excipients of ESOXIUM IT.

4.4 Special warning and precautions for use:

ESOXIUM IT Should be used with caution since it enhances action of Ach. It should not be used aimlessly for a long term when no improvement of gastrointestinal symptoms is observed. Shock and anaphylactoid reaction may occur with itopride, and the patient should be carefully monitored. If any signs of shock and anaphylactoid reaction eg hypotension, dyspnea, laryngeal edema, urticaria, pallor and diaphoresis, etc., are observed, administration of ESOXIUM IT should be discontinued and appropriate therapeutic measures should be taken.
Hepatic function disorder and jaundice with increased aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT), alanine transaminase (ALT) or serum glutamic pyruvic transaminase (SGPT) and γ-guanosine-5'-triphosphate (γ-GTP), etc., may occur, and the patient should be carefully monitored. If such abnormalities are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

Pregnancy : There are no adequate and well-controlled studies with the use of esomeprazole in pregnant women. Safe use of Itopride in pregnancy has not been established. Therefore, ESOXIUM IT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation: It is not known whether esomeprazole or itopride is excreted in human milk. No studies in lactating women have been performed. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from esomeprazole, a decision should be made whether to discontinue nursing or to discontinue ESOXIUM IT, taking into account the importance of the drug to the mother.

Use in the elderly: Since the elderly often have physiological hypofunction, adverse reactions are liable to appear. Patients receiving ESOXIUM IT, therefore, should be carefully observed, if any adverse reactions appear, appropriate measures eg, reduction or interruption of ESOXIUM IT should be taken.

Use in children: Safety and effectiveness in children has not been established.

4.5 Interaction with other medicinal products and other forms of Interactions

Esomeprazole: The decreased intragastric acidity during treatment with esomeprazole injection might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole injection. Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 eg, diazepam, citalopram, imipramine, clomipramine, phenytoin, etc, the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Concomitant oral administration of esomeprazole 30 mg resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant oral administration of esomeprazole 40 mg and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Concomitant administration of esomeprazole may reduce the plasma levels of atazanavir. Concomitant oral administration of esomeprazole 40 mg to warfarin-treated patients showed that coagulation times were within the accepted range. However, post-marketing of oral esomeprazole, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant treatment.

Concomitant oral administration of esomeprazole 40 mg and cisapride resulted in a 32% increase in AUC and a 31% prolongation of elimination t½ but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole. Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required. Co-administration of esomeprazole, clarithromycin and amoxycillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin.

Itopride: Anticholinergic drugs (eg, tiquizium bromide, scopolamine butyl bromide, timepidium bromide) may reduce pharmacological action of itopride.

4.6 Fertility, Pregnancy and lactation:

Pregnancy: There are no adequate and well-controlled studies with the use of esomeprazole in pregnant women. Safe use of Itopride in pregnancy has not been established. Therefore, ESOXIUM IT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

4.7 Effects on ability to drive and use Machines:

Not known.

4.8 Side effects:

The following is a list of possible side-effects that may occur from ESOXIUM IT Capsule. These side-effects are possible, but do not always occur. Some of the side-effects may be rare but serious.

- Flushing
- Hypertension
- Bowel irregularity
- Constipation
- Dyspepsia
- Tinnitus

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents.

4.9 OVERDOSAGE

Experience with overdosage of **ESOXIUM IT** is limited.

There have been some reports of overdosage with esomeprazole. No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein-bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase, the acid pump and inhibits both basal and stimulated acid secretion. Esomeprazole gets protonated and converted in the acidic environment of the parietal cell forming the active inhibitor, the achiral sulphonamides. By acting specifically on the proton-pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity and the effect is dose-related.

Itopride HCl increases the release of acetylcholine (Ach) through dopamine D2-receptor antagonistic action and inhibits decomposing released Ach through its acetylcholine esterase (AchE) inhibitory action, resulting in enhancement of gastrointestinal motility. When given as immediate-release form, itopride is administered as 50 mg thrice-daily (total daily dose: 150

mg). Incorporation of itopride 150 mg as sustained-release pellets makes for the release of the drug over the entire day, thus enabling once-daily administration of the formulation without compromising on the efficacy.

In gastroesophageal reflux disease (GERD), esomeprazole is required to control excessive gastric acid secretionand make the refluxate less damaging to esophageal mucosa while itopride is used to restore the competence of lower esophageal sphincter (LES) and thereby prevent reflux of gastric contents into esophagus. The 2 agents working in synergy provide complete relief from symptoms and bring about healing of the erosive lesions.

5.2 Pharmacokinetic Properties

After oral administration, peak plasma levels (Cmax) occur at approximately 1.5 hrs (Tmax). The Cmax increases proportionally when the dose is increased, and there is a 3-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 micromolar/hr/L on day 1 to 11.2 micromolar/hr/L on day 5 after 40-mg once-daily dosing. The AUC after administration of a single ESOXIUM IT 40-mg dose is decreased by 33-53% and 43-53%, respectively, after food intake compared to fasting conditions. Esomeprazole should be taken at least 1 hr before meals.
Esomeprazole is 97% bound to plasma proteins. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The major part of the metabolism is dependent on the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on the CYP3A4, which forms the sulphone metabolite. The plasma elimination half-life (t½) of esomeprazole is approximately 1-1.5 hrs. Less than 1% of parent drug is excreted in the urine. Approximately 80% of oral dose of esomeprazole is excreted as inactive metabolites in the urine and the remainder is found as inactive metabolites in the faeces.

The AUC and Cmax values were slightly higher in the elderly as compared to younger subjects at steady state. In patients with mild and moderate hepatic impairment, the AUCs were within range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2-3 times higher than in patients with normal liver function. The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered as compared to healthy volunteers.

The serum concentrations and pharmacokinetic parameters in healthy adults, after single oral administration of itopride HCl 50 mg in the fasting state are as follows: Cmax 0.28±0.02 mcg/mL, Tmax0.58±0.08 hr, AUC0-∞ 0.75±0.05 mcg.hr/mL, T½β 5.7±0.33 hr.
The concentrations reached the maximum in almost all tissues at 1-2 hrs after a single oral dose of 50 mg/kg of 14C-itopride HCl to rats, and the level at 2 hrs after administration was high in

the kidneys, small intestines, liver, adrenal glands and stomach in the order of the level (high to low) and the transfer into the central nervous system eg, brain and spinal marrow, was minimal. At a single dose of itopride HCl 100 mg orally administered to healthy adults (6 men) in the fasting state, urinary excretion rate within 24 hrs after administration was highest in the N-oxide form [67.54% of the dose (89.41% of the urinary excretion)] and in the unchanged compound was the second (4.14%) while in the others were minimal.

In the experiments using microsomes that express human CYP or flavine monooxygenase (FMO), it was found that FMO1 and FMO3 were involved in the production of main metabolic N-oxide form. However, no N-oxygenase activity of CYP1A2, 2A6, 2B6, 2C8, 2C19, 2D6, 2E1 or 3A4 was detected. Serum protein-binding ratio was 96% after oral administration at a single dose of itopride HCl 100 mg to healthy adults (6 men) in the fasting state.

Vial: Following repeated doses of 40 mg administered as IV injections, the mean peak plasma concentration is approximately 13.6 micromolar/L. The mean peak plasma concentration after corresponding oral doses is approximately 4.6 micromolar/L. A smaller increase (of approximately 30%) can be seen in total exposure after IV administration compared to oral administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the feces. Less than 1% of the parent drug is found in urine. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight.

Esomeprazole is completely metabolised by the cytochrome P-450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The parameters as follows reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers. Total plasma clearance is about 17 L/hr after a single dose and about 9 L/hr after repeated administration. The plasma elimination t½ is about 1.3 hrs after repeated once daily dosing. Total exposure (AUC) increases with repeated administration of esomeprazole. This increase is dose dependent and results in a nonlinear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration. Approximately 1-2% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of oral esomeprazole 40 mg, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for IV administration of esomeprazole.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years). The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the total exposure of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

5.3 Preclinical safety Data:

None.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Sr. No.	Ingredients	Specification
1.	Esomeprazole Magnesium Trihydrate & Itopride Hydrochloride (SR) Pellets	IH
2.	Hard Gelation Capsules	IH

6.2 Incompatibilities:

Not known.

6.3 Shelf life:

36 Months

6.4 Special precautions for storage:

Store below 30°Cin a dry place.
Keep medicines out of reach of children.

6.5 Nature and contents of container:

Alu-Alu Blister of 10 capsules, Such 3 Blisters to be packed in carton along with pack insert.

6.6 Special Precaution for Disposal and other handling:

None

7. **Marketing Authorization Holder:**

Company name: Signature Healthcare Limited

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8. **Marketing Authorization Numbers**

CTD13440

9. **Date of first Registration /renewal of the Registration:**

12/06/2026

10. **Date of revision of the text:**

12/06/2026