SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

ZOSPRIDE CAPSULES

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:
Esomeprazole magnesium Trihydrate BP eq. to Esomeprazole (As enteric coated pellets)…… 40 mg
Itopride Hydrochloride (As sustained release Pellets) ……. 150 mg

For full list of excipients, see section 6.1.

3. Pharmaceutical form:

- **Dosage Form:** Oral Capsules
- Visual **& Physical characteristics of the product:** red coloured round shaped convex enteric coated Capsules plain on both the sides.

4. Clinical particulars:

4.1 Therapeutic indications:

Used in the treatment of gastroesophageal reflux disease (acid reflux) and peptic ulcer disease.

4.2 Posology and method of administration:

Posology
Oral: One Capsules daily preferably in the morning.
Method of administration
Capsules for oral administration. The Capsules should be taken with a glass of water one hour before from meals.

4.3 Contraindications:

Hypersensitivity to the active substance. Esomeprazole should not be used Concomitantly with nelfinavir.

4.4 Special warnings and precautions for use:

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole Capsules may alleviate symptoms and delay diagnosis.

Long term use: Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On demand treatment: Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

Helicobacter pylori eradication: When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and

hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other active substances metabolised via CYP3A4 such as cisapride.

Gastrointestinal infections: Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

Absorption of vitamin B12: Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Hypomagnesaemia: Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. 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.

Risk of fracture: 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 older people 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

Esomeprazole gastro-resistant Capsules. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Sucrose: This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per Capsules, that is to say essentially 'sodium-free'.

Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this

interference, esomeprazole treatment should be stopped for at least five 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 potentiates acetylcholine action and can induce side cholinergic effects. Data about long-term administration of itopride is not available. Zospride contains lactose. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction:

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

Methotrexate: When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dosemethotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus: Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption: Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal

products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole.

Medicinal products metabolised by CYP2C19: Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with other medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine,phenytoin etc., the plasma concentrations of these active substances may be increased and a dose reduction could be needed.

Diazepam: Concomitant administration of 30 mg esomeprazole with diazepam

resulted in a 45% decrease in clearance of theCYP2C19 substrate diazepam.
Phenytoin: Concomitant administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients.

Anticholinergic agents reduce the action of itopride.

4.6 Pregnancy and lactation:

Pregnancy: Clinical data on exposed pregnancies with Esomeprazole gastro-resistant Capsules are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate normal formative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole. Safety of itopride in pregnancy has not been established. Therefore itopride can be used in pregnant women or women in whom pregnancy cannot be excluded only if therapeutic benefits considerably outweigh possible risks.

No known effect during delivery is observed.

Lactation: It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Itopride is excreted in the milk of lactating rats. Due to lack of experience with use of itopride during breast-feeding in human, a decision must be made whether to discontinue breast-feeding or to discontinue itopride therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the women.

4.7 Effects on ability to drive and use machines:

None

4.8 Undesirable effects:

Adverse reactions have been ranked according to MedDRA terminology under headings of frequency using the following convention:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

<u>Blood and lymphatic system disorders</u>

Uncommon: leukopenia*

Not known: thrombocytopenia *Careful observation should be made through haematological examination. The treatment should be discontinued when any abnormality is observed.

<u>Endocrine disorders</u>

Uncommon: hyperprolactinaemia** Not known: gynecomastia

**If e. g. galactorrhea or gynecomastia appear, the treatment must be interrupted or terminated.

<u>Gastrointestinal disorders</u>

Common: diarrhoea, constipation, abdominal pain, hypersalivation Not known: nausea
General disorders and administration site conditions
Uncommon: fatigue
Rare: Malaise, increased sweating
Hepatobiliary disorders
Not known: jaundice Immune system disorders
Uncommon: Increased liver enzymes Not known: anaphylactoid reaction
Investigations
Not known: increased level of AST, ALT, gamma-GTP, alkaline phosphatase or bilirubin
Musculoskeletal and connective tissue disorders
Uncommon: chest or back pain
Very rare: muscular weakness Nervous system disorders
Uncommon: headache, sleep disorders, dizziness Not known: tremor
Psychiatric disorders Uncommon: irritability, insomnia
Very rare: aggression, hallucinations
Renal and urinary disorders
Uncommon: BUN (blood urea nitrogen) and creatinine increased
Skin and subcutaneous tissue disorders
Rare: rash, erythema, pruritus

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 Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose:

There is very limited experience to date with deliberate overdose of esomeprazole. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Overdose of itopride was not experienced in humans. In case of overdose the standard supportive measures as gastric lavage and symptomatic therapy should be applied.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Esomeprazole:

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors,

ATC Code: A02B C05

Pharmacodynamics:

Mechanism of action

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. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

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.

Itopride:

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, Propulsives; ATC code: A03FA07

Itopride activates the gastrointestinal propulsive motility by dopamine D2 receptors antagonistic action and acetylcholine esterase inhibitory action. Itopride activates acetylcholine release and inhibits its degradation.

In addition itopride has an antiemetic effect which is based on interaction with dopamine D2 receptors in chemoreceptor zone. This effect was demonstrated by dose dependent inhibition of apomorphine induced vomiting in dogs.

Itopride accelerates stomach emptying in humans.

In animal studies in dogs with a single dose administration itopride supported stomach emptying.

Itopride has high specific action in upper part of gastrointestinal tract.

Itopride does not influence plasma concentrations of gastrin.

5.2 Pharmacokinetic properties:

Absorption: Esomeprazole is acid labile and is administered orally as enteric-coated granules in a Capsules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Itopride is absorbed rapidly and almost completely from gastrointestinal tract. Relative bioavailability is about 60% due to first-pass effect. Food does not affect bioavailability of the medicinal 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: The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight.Esomeprazole is 97% plasma protein bound. About 96% of itopride is bound to plasma proteins, mainly albumin. Alpha-1-acid-glycoprotein accounts for less than 15% of binding.

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% vs. 96%). Penetration into the central nervous system was minimal. Itopride is excreted in milk of lactating rats.

Metabolism: Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethylmetabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.
In humans, itopride is extensively metabolised in liver. Three metabolites were identified of which only one manifests minor activity without pharmacological significance (about 2 to 3% of itopride effect). The main metabolite is N-oxide, which is product of oxidation of the tertiary amine-N-dimethyl group.
Itopride is metabolised by flavine monooxygenase (FMO3). The amount and efficacy of human FMO isoenzymes can be associated with genetic polymorphisms which can result in rare autosomal recessive condition known as trimethylaminuria (fish odour syndrome). Biological half-life in patients with trimethylaminuria can be longer.
Pharmacokinetic in vivo studies of CYP-mediated reactions did not prove inhibition or induction of CYP2C19 and CYP2E1 caused by itopride. Administration of itopride did not influence content of CYP or the activity of uridine-diphosphate-glucuronyl transferase.

Excretion: The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.
Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily 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 faeces. Less than 1% of the parent drug is found in urine.
Itopride and its metabolites are primarily excreted by urine. The amount of excreted itopride and N-oxide after oral single therapeutic dose to healthy volunteers was 3.7% and 75.4%, respectively. Half-life of itopride is about 6 hours.

6. Pharmaceutical particulars:

6.1 List of Excipients:

1	Hard gelatin capsule, yellow size "0"	IH

6.2 Incompatibilities:
Not Applicable

6.3 Shelf life:
36 Months

6.4 Special precautions for storage:
Keep the blister in the carton to protect from light and moisture.

6.5 Nature and contents of container:

Alu-alu

Pack Size: 3 x 10

6.6 Special precautions for disposal:

No special instructions needed

7. Marketing Authorization Holder

CURIS LIFESCIENCES PVT. LTD. REGD. OFFICE:

Name **:** Curis Lifesciences Pvt. Ltd.

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8. Marketing Authorisation number

H2022/CTD6431/2143ER

9. Date of revision of the text

14/02/2022

10. Dosimetry (If Applicable):

07/09/2026