SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zosperide Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Esomeprazole 40mg & Itopride 150mg as Sustained Release

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained release capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrointestinal symptoms of functional, non-ulcer dyspepsia, like feelings of bloating, gastric fullness, discomfort to pain in epigastrium, anorexia, heartburn, nausea and vomiting.
The medicinal product is intended for adults.
Esomeprazole Jubilant gastro-resistant tablets are indicated in adults for:

Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- healing of *Helicobacterpylori*associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacterpylori associated ulcers*

Patients requiring continued NSAID therapy
- Healing of gastric ulcers associated with NSAID therapy.
- Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Prolonged treatment after i.v. induced

prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

Esomeprazole Jubilant gastro-resistant tablets are indicated in adolescents from the age of 12 years for:

Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacterpylori*

4.2 Posology and method of administration

Posology
The recommended dose for adults is 150 mg daily, i.e. 1 tablet 3 times a day before meal.
This dose can be reduced if required in the course of disease. The exact dosage and duration of treatment depends on the clinical state of the patient. The duration of the administration in clinical studies was maximally 8 weeks.

Paediatric population
The safety and efficacy of Itoprid PMCS in paediatric population has not been established.

Hepatic or renal impairment
Itopride is metabolized in liver. Itopride and its metabolites are excreted mainly via kidneys. Patients with reduced hepatic or renal functions should be carefully monitored and in case of adverse reactions it is necessary to take appropriate measures, as e.g. to reduce the dosage or to discontinue the therapy.

Elderly
It was shown in clinical studies that the incidence of adverse effects in patients aged 65 years and older was not higher than in younger patients. Itopride should be administered in elderly patients with adequate caution because of increased incidence of hepatic and renal function disorders, other diseases or treatment with additional drugs.

Method of administration

Tablets should be swallowed whole with a sufficient amount of liquid.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Itoprid PMCS 50 mg should not be used in patients in whom increased gastrointestinal motility could be harmful, e.g. in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Itopride potentiates acetylcholine action and can induce side cholinergic effects. Data about long-term administration of itopride is not available.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per one film-coated tablet, that is to say essentially 'sodium-free'.

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), healthcare 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 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 Esomeprazole Jubilant. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products
Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). 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 (see section 4.5). 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 (see section 4.5).

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 5 days before CgA measurements (see section 5.1). 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.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.
Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms.

Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed.
Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

Sucrose:
This medicine contains sucrose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction was detected when itopride was administered concomitantly with warfarin, diazepam, diclofenac, ticlopidine, nifedipine and nicardipine. Drug-drug interactions that arise due to cytochrome P450 metabolism are not assumed because itopride is metabolised mainly by flavine monooxygenase.
Itopride has gastrokinetic effect that could influence the absorption of concomitantly orally administered medicines. Particular attention should be paid to medicines with a narrow therapeutic index, medicines with prolonged-release of the active substance and enteric-coated drug formulations. Anticholinergic agents may reduce the action of itopride. Substances as cimetidine, ranitidine, tepronone and cetrexate do not affect prokinetic activity of itopride.

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety of itopride in pregnancy was not verified. Therefore itopride can be used in pregnant women or women in that pregnancy cannot be excluded only if therapeutic benefits outweigh possible risks considerably.

Breast-feeding
Data about excretion in mother milk is known only in animals. Because of lack of experience with use of itopride during breast-feeding itopride it is not recommended for breast-feeding women.

Effects ofe someprazole on the pharmacokinetics of other drugs

Protease inhibitors
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax and Cmin).
Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300
mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, Cmax and Cmin by 36–39 % and mean AUC, Cmax and Cmin for the pharmacologically

active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section 4.4) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate 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. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients.
Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma
concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Diazepam
Concomitant administration of 30 mg esomeprazole resulted in a 45%

decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin
Concomitant administration of 40 mg esomeprazole 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.

Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUCτ by 15% and 41%, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride
In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t1/2) 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 (see also section 4.4).

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range.
However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o.daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the

same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction

Amoxicillinand quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Naproxenor rofecoxib
Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCτ by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4
Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Paediatric population
Interaction studies have only been performed in adults.

4.7 Effects on ability to drive and use machines

Although no effects on ability to drive and use machines have been found, impairment of alertness cannot be ruled out since dizziness may occur very rarely.

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).

Blood and lymphatic system disorders *Uncommon:*
Leucopenia*.

Tabulated list of adverse reactions
The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency very common > 1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 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).

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section 4.4); hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia m be associated with hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrh flatulence, nausea/vomiting, fundic g polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidias
	Not known	Microscopic colitis

Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johns syndrome, toxic epidermal necrolysis drug reaction with eosinophilia and systemic symptoms (DRESS)
	Not known	Subacute cutaneous lupus erythema (see section 4.4)
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (se section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patient failure has been reported concomitar
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

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

Immune system disorders
Not known: Anaphylactoid reaction.

Endocrine disorders
Uncommon: Hyperprolactinaemia**.
Not known: Gynecomastia.
**If i. g. galactorrhea or gynecomastia appeal the treatment must be interrupted or terminated.

Psychiatric disorders
Uncommon: Irritability.

Nervous system disorders
Uncommon: Headache, sleep disorders, dizziness.
Not known: Tremor.

Gastrointestinal disorders
Uncommon: Diarrhoea, constipation, abdominal pain, hypersalivation.
Not known: Nausea.

Hepatobiliary disorders
Not known: Jaundice.

Skin and subcutaneous tissue disorders *Rare:* Rash, erythema, pruritus.

Musculoskeletal and connective tissue disorders *Uncommon:* Chest or back pain.

Renal and urinary disorders
Uncommon: BUN (blood urea nitrogen) and creatinine increased.

General disorders and administration site conditions *Uncommon:* Fatigue.

Investigations
Not known: AST increased, ALT increased, gama-GTP increased, alkaline phosphatase increased, bilirubine increased.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdose was not experienced in humans. In case of overdose the usual measures of gastric lavage and symptomatic therapy should be applied. There is very limited experience to date with deliberate overdose. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for functional gastrointestinal disorders, propulsives, ATC code: A03FA07 & A02B C05

Mechanism of action
Itopride activates the gastrointestinal propulsive motility by dopamine D_2 receptors antagonistic action and acetylcholine esterase inhibitory action. Itopride activates acetylcholine release and inhibits its degradation.
In addition itopride has an antiemetic action which is based on interaction with dopamine D_2 receptors
in chemoreceptor zone. This action 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.

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.

Mechanism of action
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.

Pharmacodynamic effects
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%.
Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.
After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10 % respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389).

Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group 7.7% vs 13.6%.

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Clinical efficacy

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

5.2 Pharmacokinetic properties

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 ($Vd_{ß}$ = 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.

Biotransformation
Itopride is extensively metabolised in liver in humans. Three metabolites were identified of which only one manifests minor activity without pharmacological significance (about 2 to 3% of itopride effect).
Itopride is metabolised by flavine monoxygenase (FMO3). The amount and effectivity of human FMO
isoenzymes can be associated with genetic polymorphism 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 CYP2C19 and CYP2E1 caused by itopride.
Administration of itopride did not influence content of CYP or the activity of uridine-diphosphate-glucuronyl transferase.

Elimination
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%, respective 75.4%.
Half-life of itopride is about 6 hours.

Esomeprazole
Absorption
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *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.

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.

Biotransformation
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 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.

Elimination
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.

Linearity/non-linearity
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma
concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Special patient populations

Poor metabolisers
Approximately 2.9±1.5% 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 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

Gender
Following a single dose of 40 mg esomeprazole the mean are under the plasma concentration-time curve is approximately 30% higher in females

than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

Hepatic impairment

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 area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum 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.

Renal impairment

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.

Older people

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Paediatric population

Adolescents12-18 years:

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (tmax) in 12 to18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Oral single lethal dose was 2000 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 cancerogenity 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 after were observed. Prolongated precoital interval was observed at doses 300 mg/kg/day. No side effect on copulation and fertility was proved.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinized maize
starch Croscarmellose
sodium Colloidal silicon
dioxide Magnesium
stearate
Coating composition Opadry II White
85F18422: Partially hydrolyzed
polyvinyl alcohol Titanium dioxide
Macrogol
3350 Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/Al blister or PVC/PVdC/Al blister, carton.
Pack size: 10, 20, 30, 40, 90, 100 or 120 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sai Pharmaceuticals Limited
Whitefield Edge, at the junction of James Gichuru Road
Ole Nguruone Road in Lavington, Nairobi, Kenya
Landline: +254 20 4454301 / 2
Mobile: +254 721 243 322
Email: info@saipharm.com
Postal Address: P.O. Box 66551, Nairobi, 00800, Kenya
Official Website: saipharm.com

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD6431/2143ER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th August 2026

10. DATE OF REVISION OF THE TEXT

30th August 2026