Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ESOGLAX 40-D 40/30 mg hard gelatin Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Esomeprazole Magnesium Trihydrate USP Eq. to Esomeprazole 40 mg (As enteric coated pellets)

Domperidone BP 30 mg (As sustained release pellets)

For the full list of excipients, see Section 6.1

3. Pharmaceutical form

Oral Capsule

Orange and white colour spherical pellets filled in "2" size hard gelatin capsule having a yellow body and a yellow coloured cap.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of adult patients with gastroesophageal reflux disease (GERD) not responding to esomeprazole alone.

4.2 Posology and method of administration

Posology

It is recommended to take ESOGLAX-40 D Capsules 1 hour before meals.

Special population

Renal impairment

Dose adjustment is not required in all patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution. Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded. Domperidone is contraindicated in moderate or severe hepatic impairment. Dose modification in mild hepatic impairment is however, not needed.

Geriatric population

Dose adjustment is not required in the elderly.

Pediatric Population

Safety and effectiveness of Esomeprazole & Domperidone Capsules in pediatric patients have not been established

Method of administration

Recommended dose for adults is 1 capsule to be administered once daily for 4 to 8 weeks

The capsules should be swallowed whole with liquid. The capsules should not be opened or chewed, or crushed.

Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted, and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose

Capsules should be administered on an empty stomach, preferably in the morning or at least 1 hour prior to a meal.

4.3 Contraindications

Esomeprazole

Hypersensitivity to the active substance, to substituted benzimidazoles, or to any of the excipients.

Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

Esomeprazole should not be used concomitantly with nelfinavir and rilpivirine-containing products.

Domperidone

Domperidone is contraindicated in the following situations:

• Known hypersensitivity to domperidone

• Prolactin-releasing pituitary tumour (prolactinoma).

• When stimulation of the gastric motility could be harmful, e.g., in patients with gastrointestinal haemorrhage, mechanical obstruction, or perforation.

• in patients with moderate or severe hepatic impairment.

• in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances, or underlying cardiac diseases such as congestive heart failure.

• co-administration with QT-prolonging drugs, at the exception of apomorphine.

• co-administration with potent CYP3A4 inhibitors.

• In patients with gastrointestinal hemorrhage, mechanical obstruction, or perforation (i.e., when stimulation of the gastric motility could be harmful).

• In patients with moderate or severe hepatic impairment

4.4 Special warnings and precautions for use

Esomeprazole

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 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.

Gastrointestinal Infections

Treatment with proton pump inhibitors may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

Absorption of Vitamin B12

Esomeprazole, like 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 (e.g., longer than 3 years).

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 medicinal products 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 the 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. SCLE after previous treatment with a proton

pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI-associated SLE is usually milder than non-drug-induced SLE. Onset of SLE typically occurs within days to years after initiating treatment, primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving esomeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive, and elevated serological test results may take longer to resolve than clinical manifestations.

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Clostridium difficile-Associated Diarrhea

Published observational studies suggest that PPI therapy, like esomeprazole, may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported

with the use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole, refer to Warnings and Precautions section of the corresponding prescribing information.

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic, and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Combination with other medicines

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 medicinal products 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. Drugs that induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole with St. John's Wort or rifampin. Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

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.

If CgA and gastrin levels have not returned to the reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Domperidone

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors. Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older. Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

Domperidone is contraindicated with QT-prolonging drugs, including apomorphine, unless the benefit of the coadministration with apomorphine outweighs the risks, and only if the recommended precautions for coadministration mentioned in the apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.

Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily, depending on the severity of the impairment. The dose may also need to be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Esomeprazole

- *Interference with Antiretroviral Therapy*

Reduced Concentrations of Atazanavir and Nelfinavir: Concomitant use of atazanavir and nelfinavir with PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. If the combination of atazanavir with a PPI is 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.

Increased Concentrations of Saquinavir: Co-administration of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with other antiretroviral drugs, too. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. 2)

- *Drugs for Which Gastric PH Can Affect Bioavailability (ketoconazole, atazanavir, iron salts, erlotinib, mycophenolate mofetil, digoxin)*

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability. Like with other drugs that decrease intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole.

Digoxin: Concomitant treatment with omeprazole (20 mg daily), of which esomeprazole is an enantiomer, and digoxin in healthy subjects increased

the bioavailability of digoxin by 10%. Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

Mycophenolate Mofetil (MMF): Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF.

- *Effects on Hepatic Metabolism/ Cytochrome P-450 Pathways*

Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. In-vitro and in-vivo studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole 5 does not have any clinically significant interactions with quinidine, clarithromycin, or amoxicillin.

Warfarin: Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR (International Normalized Ratio) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding.

Clopidogrel: Avoid concomitant use of esomeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by the use of concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with esomeprazole 40 mg reduces the pharmacological activity of clopidogrel. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged, or when using esomeprazole, consider alternative antiplatelet therapy.

Diazepam: Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

Phenytoin: Concomitant administration of esomeprazole 40 mg 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.

Cilostazol: Omeprazole, as well as esomeprazole, act as inhibitors of CYP2C19. Omeprazole, of which esomeprazole is an enantiomer, 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 esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (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.

Voriconazole: Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP3A4, such as voriconazole, may result in a more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses (up to 240 mg/day), dose adjustment may be considered.

Rifampicin: Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Avoid concomitant use of rifampin with esomeprazole.

St. John's Wort: Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's wort, an inducer of CYP3A4. Avoid concomitant use of St. John's wort with esomeprazole.

- *Concomitant Administration with Other Drugs*

Tacrolimus: Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

Combination Therapy with Clarithromycin: Co-administration of esomeprazole, clarithromycin, and amoxicillin has increased plasma levels of esomeprazole and 14-hydroxyclarithromycin.

Methotrexate: Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, leading to a risk of methotrexate toxicity. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

- *Drug / Laboratory Tests Interactions*

Interactions with Investigations of Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false-

positive results in diagnostic investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements; consider repeating the test if initial CgA levels are high.

Domperidone

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

There is an increased risk of the occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

- *Concomitant use of the following drugs is contraindicated.*

QTc-prolonging medicinal products:
- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine).
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antipsychotics (e.g., haloperidol, pimozide, sertindole).
- Certain antidepressants (e.g., citalopram, escitalopram).
- Certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin).
- Certain antifungal agents (e.g., pentamidine).
- Certain antimalarial agents (e.g., halofantrine, lumefantrine).
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride).
- Certain antihistaminics (e.g., mequitazine, mizolastine).
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine).
- Other medicines (e.g., bepridil, diphemanil, methadone).

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects):

- Protease inhibitors.
- Systemic azole antifungals.
- Some macrolides (e.g., erythromycin, clarithromycin, and telithromycin).

- *Concomitant use of the following drugs is not recommended.*

Moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and some macrolides). 7

- *Concomitant use of the following drugs requires caution.*

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: Azithromycin and roxithromycin.

Ketoconazole/Erythromycin and QTc Prolongation: Separate in vivo pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4-mediated first-pass metabolism by these drugs (as both of these drugs significantly inhibit the CYP3A4 enzyme). Both the Cmax and AUC of domperidone at steady state were increased approximately threefold in each of these interaction studies. In these studies, concomitant use of domperidone and ketoconazole or erythromycin resulted in an increase in QTc over the observation period.

4.6 Pregnancy and Lactation

Pregnant Women

Esomeprazole: Pregnancy Category C; Domperidone: Pregnancy Category C. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to reproductive toxicity (embryonal/fetal development). Also, animal studies with the racemic mixture (i.e., omeprazole) do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of esomeprazole.

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses. There are however, no adequate and well controlled studies available for use of esomeprazole with domperidone combination therapy during pregnancy. Thus, it is recommended that during pregnancy, ESOGLAX 40-D Capsules should be used with caution and only if clearly needed.

Lactating Women

Esomeprazole is likely to present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants.

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. Caution should be exercised in case of QTc prolongation risk

factors in breast-fed infants. ESOGLAX 40-D Capsules should not be used during breastfeeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue/abstain from therapy, taking into account the benefit of the drug to the mother.

Fertility

Animal studies with the racemic mixture of omeprazole, given by oral administration, do not indicate effects with respect to fertility

4.7 Effects on the ability to drive and use machines

Esomeprazole

Esomeprazole has a minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) have been reported. If affected patients should not drive or use machines.

Domperidone

Domperidone has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Esomeprazole

Summary of the safety profile

Headache, abdominal pain, diarrhoea, and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse medicinal product reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: 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).

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
	Not known	Systemic lupus erythematosus
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
	Common	Headache
Nervous system disorders	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis, pancreatitis
	Uncommon	Increased liver enzymes

Hepatobiliary disorders	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-Johnson syndrome, toxic epidermal necrolysis (TEN)
	Not known	Subacute cutaneous lupus erythematosus, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist, or spine
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis: in some patients, renal failure has been reported concomitantly
	Not known	Acute kidney injury
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Pediatrics

Safety and effectiveness of esomeprazole in pediatric patients have not been established.

Domperidone

Tabulated list of adverse reactions

The safety of domperidone was evaluated in clinical trials and in postmarketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), irritable bowel syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of domperidone base. The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism

were excluded.
The following terms and frequencies are applied:
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), Where frequency cannot be estimated from clinical trials data, it is recorded as “Not known”.

System Organ Class	**Adverse Drug Reaction Frequency**		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsade de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticaria Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

In 45 studies where domperidone was used at higher dosages, for longer duration, and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

4.9 Overdose

Esomeprazole

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole. 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. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.

Domperidone

Symptoms
Symptoms of overdose may include agitation, altered consciousness, convulsions, disorientation, somnolence, and extrapyramidal reactions.

Treatment
There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal may be useful. ECG monitoring should be undertaken because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Esomeprazole

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

ATC code: A02B C05

Esomeprazole is the S-isomer of omeprazole. Esomeprazole reduces gastric acid secretion through a specific targeted mechanism of action, i.e., inhibition of the acid pump in the gastric parietal cell. Both the R- and S-isomers 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.

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 5 days, the mean peak acid output decreases by 90% when measured 6 to 7 hours after dosing on day five. After 5 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, was 76%, 54%, and 24% for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97%, 92%, and 56%. Esomeprazole increases the mean fasting gastrin level in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Domperidone

Pharmacotherapeutic class: Dopamine antagonist with anti-emetic properties
ATC code: A03FA03

Prokinetic Effect: The prokinetic (gastrokinetic) properties of domperidone are related to its peripheral dopamine receptor blocking action.

Antiemetic Effect: Domperidone produces an antiemetic effect by blocking dopamine receptors (D2) peripherally. Inhibition of peripheral D2 receptor signaling prevents or relieves various GI symptoms, such as nausea and vomiting, and also relieves reflux and other symptoms associated with upper GI disorders.

Clinical efficacy

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

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 the 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 medicinal product is found in urine.

Linearity/non-linearity
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. 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 populations

Poor metabolisers
Approximately 2.9 ±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg oral esomeprazole, 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%. These findings have no implications for the posology of esomeprazole.

Gender
Following a single oral dose of 40 mg esomeprazole the mean total

exposure 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.

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

Pediatric population
No relevant data is available for esomeprazole in pediatric population.

Domperidone

Absorption
Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.
The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is

slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution
Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.
Metabolism
Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion
Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

<u>Special population</u>
Hepatic impairement

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax

and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment.

Renal impairment
In subjects with severe renal insufficiency (creatinine clearance < 30 mL/min/1.73 m2), the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency.
However, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric population
No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Animal Toxicology or Pharmacology

Esomeprazole
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.

Domperidone

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-fold, based on IC50 values inhibiting currents through IKr ion channels in
comparison to the free plasma concentrations in humans after

administration of the maximum daily dose of 10 mg administered 3 times a day. Safety margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45-fold. Safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45-fold. In in vivo models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold.
At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. Pharmaceutical Particulars

6.1 List of Excipients

None

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 months

6.4 Special precautions for storage

Stored at a temperature not exceeding 30°C, in a cool dry place and protect from sun light.

6.5 Nature and content of the container

10 capsules are packed in an Alu-Alu blister, and 3 such blisters are packed in a carton along with a package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

GALAXY PHARMACEUTICAL LTD
1st floor, Doctors Park, 3rd Parkland Avenue, Nairobi. Kenya.
PO.BOX:39107-00623
KENYA
Telephone: 020-3748551/2/3/4
Telefax: N/A
E-Mail: info@galaxypharma.co.ke

8. Marketing Authorization Number

CTD10085

9. Date of first authorization/renewal of the authorization

25/03/2023

10. Date of revision of the text

12/05/2025