Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Rebiweb D (Domperidone 30 mg and Rabeprazole 20 mg) Hard Gelatin Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains: Enteric coated Rabeprazole Sodium 20mg, sustained release Domperidone 30mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Green/ Transparent Hard Gelatin shell size '2'
Each capsule contains reddish brown, orange, and white colour pellets.

4. Clinical particulars

4.1 Therapeutic indications

- Duodenal and gastric ulcer
- Gastroesophageal reflux disease (GERD).
- Zollinger-Ellison Syndrome
- In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter *pylori* (H. *pylori*) in patients with peptic ulcer disease. See section 4.2.
- Nausea associated with acid peptic disorders.

4.2 Posology and method of administration

Duodenal Ulcer and Gastric Ulcer: The recommended oral dose for both duodenal ulcer and gastric ulcer is 20 mg to be taken once daily in the morning. Most patients with duodenal ulcer heal within four weeks. However again a few patients may require an additional six weeks of therapy to achieve healing.

GERD: The recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks. For long-term management, a maintenance dose of *Rebiweb D* 20 mg once daily can be used depending upon patient response.

Zollinger-Ellison Syndrome: Treatment should continue as clinically indicated.

Eradication of H. pylori: Patients with H. pylori infection should be treated with eradication therapy. The following combination given for 7 days is recommended. *Rebiweb D* twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.

For indications requiring once daily treatment *Rebiweb D* Capsules should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

Nausea associated with acid peptic disorders: Adults and adolescents (12 years of age and older and weighing 35 kg or more): One Capsule per day.

Hepatic Impairment
Rebiweb D is contraindicated in moderate or severe hepatic impairment (see section 4.3). Dose modification in mild hepatic impairment is however not needed (see section 5.2).

Renal impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of *Rebiweb D* should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see sections 4.4 and 5.2).

Children
Rebiweb D is not recommended for use in children, as there is no experience of its use in this group.

Method of administration
Patients should be cautioned that the *Rebiweb D* Capsules should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Rebiweb D is contra-indicated in pregnancy and during breast feeding (see section 4.6).

Known hypersensitivity to domperidone or any of the excipients.

Prolactin-releasing pituitary tumour (prolactinoma).

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

In patients with moderate or severe hepatic impairment (see section 5.2).

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 (see section 4.4)

Co-administration with QT-prolonging drugs, at the exception of apomorphine (see sections 4.4 and 4.5)

Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5)

4.4 Special warnings and precautions for use

Special warnings and precautions for use of Rabeprazole
Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with RABEPRAZOLE.

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

A risk of cross-hypersensitivity reactions with another proton pump inhibitor (PPI) or substituted benzimidazoles cannot be excluded.

Patients should be cautioned that Capsule should not be chewed or crushed but should be swallowed whole.

RABEPRAZOLE is not recommended for use in children, as there is no experience of its use in this group.

There has been post marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). In most cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In most cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However, because there are no clinical data on the use of RABEPRAZOLE in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with RABEPRAZOLE is first initiated in such patients.

Co-administration of atazanavir with RABEPRAZOLE is not recommended (see section 4.5).

Treatment with PPIs, including RABEPRAZOLE, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile (see section 5.1).

PPIs, 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 older people or in presence of other recognised risk factors. Observational studies suggest that PPIs 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.

Severe hypomagnesaemia has been reported in patients treated with PPIs like RABEPRAZOLE 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.

Concomitant use of rabeprazole with methotrexate: 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.

Influence on vitamin B12 absorption: Rabeprazole sodium, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or a- chlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Subacute cutaneous lupus erythematosus (SCLE): PPIs are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional

should consider stopping RABEPRAZOLE. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

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

Renal impairment
Rabeprazole: Acute tubulointerstitial nephritis (TIN) has been observed in patients taking rabeprazole and may occur at any point during rabeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure. Rabeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Special warnings and precautions for use of Domperidone

Cardiovascular effects of Domperidone
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 (see section 4.8).
Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). 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 (see section 4.3.). 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.

Domperidone Use with apomorphine.

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

Renal impairment
Domperidone: 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

Interactions of Rabeprazole
Rabeprazole sodium produces a profound and long-lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with RABEPRAZOLE.

In clinical trials, antacids were used concomitantly with the administration of RABEPRAZOLE and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other PPIs. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir (see section 4.4).

Methotrexate: Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see

methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Interactions of 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.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of Domperidone with the following substances 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 anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g. , erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see section 4.3).
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC.

Domperidone and Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:
- Protease inhibitors
- Systemic azole antifungals
- Some macrolides (erythromycin, clarithromycin, telithromycin) (see section 4.3).

Concomitant use of Domperidone with the following substances is not recommended.

- Moderate CYP3A4 inhibitors i.e., diltiazem, verapamil, and some macrolides. (See section 4.3)

Concomitant use of Domperidone with the following substances requires caution in use.
Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.
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.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies.

In these studies, domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Rabeprazole: There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. RABEPRAZOLE is contraindicated during pregnancy.

Domperidone: 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 (see section 5.3). Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding
Rabeprazole: It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in breast feeding women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore, RABEPRAZOLE should not be used during breast feeding.

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. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

4.7 Effects on ability to drive and use machines.

Rabeprazole: Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that rabeprazole would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

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

4.8 Undesirable effects

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Tabulated list of adverse reactions of Rabeprazole

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketing experience.

Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (>1/10,000, <1/1000) very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations	Infection				
Blood and the lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity1,2		
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia4
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral Oedema
Respiratory, thoracic, and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic Gland Polyps (Benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalopathy3		
Skin and subcutaneous tissue disorders		Rash Erythema2	Pruritus Sweating Bullous reactions2	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus4
Musculoskeletal connective tissue and bone disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine 4			
Renal and urinary disorders		Urinary tract infection	Tubulointerstitial nephritis (with possible		

			progression to renal failure)		
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes3	Weight increased		

1: Includes facial swelling, hypotension and dyspnoea

2: Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

3: Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with RABEPRAZOLE is first initiated in such patients (see section 4.4).

4: See Special warnings and precautions for use (4.4)

Tabulated list of adverse reactions of Domperidone

The safety of Domperidone was evaluated in clinical trials and in post marketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GERD), 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 (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 (see section 4.4)			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.

Reporting of suspected adverse reactions of Domperidone
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.

4.9 Overdose

Symptoms of Rabeprazole sodium of Overdose: Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Symptoms of Domperidone Overdose: Symptoms of over dosage may include agitation, altered consciousness, convulsions, disorientation, somnolence, and extrapyramidal reactions**.**

Treatment of Domperidone Overdose: 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Rabeprazole sodium: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), PPIs, ATC code: A02B C04
Domperidone: Propulsives, ATC code: A03F A 03

Mechanism of action
Rabeprazole sodium
Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump) The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.
Anti-secretory activity: After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days. Decreased gastric acidity due to any means, including PPIs such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may possibly increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Serum gastrin effects: In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting

the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy. Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of H. pylori infection. In over 250 patients followed for 36 months of continuous therapy, no significant change in findings present at baseline was observed.

Other effects: Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone. Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal H. pylori infection.

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 PPIs 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.

<u>Domperidone</u>
Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

Clinical study in infants and children 12 years of age and younger

Paediatric population for rabeprazole sodium
A multicentre, double-blinded, randomised, placebo-controlled, parallel-group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomised subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing vomiting episode during the first 48 hours after the first treatment administration (see section 4.2).

5.2 Pharmacokinetic properties

Absorption
RABEPRAZOLE is an enteric-coated (gastro-resistant) formulation necessary because it is acid-labile. Absorption of rabeprazole therefore begins only after the capsule leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. There was no clinically

relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

DOMPERIDONE is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The Cmax 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
Rabeprazole is approximately 97% bound to human plasma proteins.
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 and Excretion

Rabeprazole sodium, as is the case with other members of the PPI class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in vitro studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.
Following a single 20 mg ^{14}C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of

the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.
There are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.
Elimination of rabeprazole was somewhat decreased in older people. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60% and $t_{½}$ increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.
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.

Domperidone: 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.

Hepatic impairment
Rabeprazole sodium: Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Domperidone: In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} 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 C_{max} 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 (see section 4.3).

Renal impairment

Rabeprazole sodium: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5ml/min/1.73 m^2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.
Domperidone: In subjects with severe renal insufficiency (creatinine clearance <30ml/min/1.73m^2) 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.

CYP2C19 polymorphism: Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and $t_{½}$ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst C_{max} had increased by only 40%.

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

5.3 Preclinical safety data

Preclinical safety data for Rabeprazole
Non-clinical effects were observed only at exposures sufficiently more than the maximum human exposure that make concerns for human safety negligible in respect of animal data.
Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

Preclinical safety data for 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
Dummy Pellets
Empty green/transparent hard gelatin capsule shell size “2”

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage:
Store below 30℃

6.5 Nature and contents of container
Alu – Alu blister pack of 1 x 10 Hard Gelatin Capsules, packed in an outer carton.

6.6 Special precautions for disposal and other handling:
No special requirements.

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

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Swanira Lifesciences Pvt. Ltd
Address: GIDC Ankleshwar -393002, Gujarat, India

Manufacturing site address:
Ethicare Pharmaceuticals (P) Ltd,
Address: 307, GIDC, Por-Ramangamdi District Vadodara,
Gujarat, 392243 India.

Local Technical Representative:
Pharmweb Chemist
Address: Kirk House Building, Duruma Road, 3rd floor, room No: D9. P.O. Box 17170-00100 Nairobi, Kenya

8. Marketing authorization number
CTD9457

9. Date of first registration
28-Aug-2023

10. Date of revision of the text:
12-Sep-2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable