Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

ESODOME

2. Qualitative and quantitative composition

Each enteric coated tablet contains:

Esomeprazole Magnesium Trihydrate Eq. To Esomeprazole 20 mg

Domperidone 10 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Blue colour, circular, biconvex, enteric coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Esomeprazole Enteric coated tablets are indicated in adults for:

Gastroesophageal Reflux Disease (GERD)

treatment of erosive reflux esophagitis

Long-term management of patients with healed esophagitis to prevent relapse

symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and

healing of *Helicobacter pylori-associated* duodenal ulcers and

prevention of relapse of peptic ulcers in patients with *Helicobacter pylori-associated* ulcers. Patients requiring continued NSAID therapy healing of gastric ulcers associated with NSAID therapy.

prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk. Treatment of Zollinger Ellison Syndrome

Esomeprazole Enteric coated tablets are indicated in adolescents from the age of 12 years for:

Gastroesophageal Reflux Disease (GERD)

treatment of erosive reflux esophagitis

long-term management of patients with healed esophagitis to prevent relapse

symptomatic treatment of gastroesophageal reflux disease (GERD)

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

Domepridone is indicated for:

the relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

Esomeprazole

- Posology

Adults

Gastroesophageal Reflux Disease (GERD)

treatment of erosive reflux esophagitis 40 mg once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have

persistent symptoms.

long-term management of patients with healed esophagitis to prevent relapse 20 mg once daily.

symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. An on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and

healing of *Helicobacter pylori* associated duodenal ulcer and

prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers 20 mg Esomeprazole with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy

healing of gastric ulcers associated with NSAID therapy:

The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: 20 mg once daily.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is Esomeprazole 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Special Populations Renal impairment

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

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 (see section 5.2).

Elderly

Dose adjustment is not required in the elderly. Paediatric population

Adolescents from the age of 12 years Gastroesophageal Reflux Disease (GERD)

treatment of erosive reflux esophagitis 40 mg once daily for 4 weeks

An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

long-term management of patients with healed esophagitis to prevent relapse 20 mg once daily.

symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be

further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily.

Treatment of duodenal ulcer caused by Helicobacter pylori

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

The posology recommendation is:

Weight	Posology
30 - 40 kg	Combination with two antibiotics: Esomeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.
> 40 kg	Combination with two antibiotics: Esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

Children below the age of 12 years

For posology in patients aged 1 to 11 reference is made to the Esomeprazole sachet SmPC. Method of administration

The Enteric coated tabletsshould be swallowed whole with liquid. The Enteric coated tabletsshould not be chewed or crushed. For patients who have

difficulty in swallowing, the Enteric coated tabletscan also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the Enteric coated tabletsdisintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the Enteric coated tabletscan be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested. For preparation and administration instructions see section 6.6.

Domepridone

Domeperidone should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

It is recommended to take oral domperidone tablets before meals. If taken after meals, absorption of the drug is somewhat delayed.

Patients should try to take each dose at 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.

Usually, the maximum treatment duration should not exceed one week.

See section 4.4. for further information.

Adults and adolescents (12 years of age and older and weighing 35 kg or more)

One 10mg tablet up to three times per day with maximum dose of 30 mg per day.

Hepatic Impairment

Domperidone 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 Domperidone tablets 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)

Paediatric population

The efficacy of Domperidone in children less than 12 years of age has not been established (see section 5.1).

The efficacy of Domperidone in adolescents 12 years of age and older and weighing less than 35 kg has not been established.

Method of administration

Domperidone 10mg Tablets are for oral administration

4.3 Contraindications

Esomeprazole

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed in section 6.1. Esomeprazole should not be used concomitantly with nelfinavir (see section 4.5).

Domepridone

Domperidone is contraindicated in the following situations:

• 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 section 4.4 and 4.5).

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

• Known hypersensitivity to domperidone or any of the excipients.

• Prolactin-releasing pituitary tumour (prolactinoma.)

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

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.

Helicobacter pylori eradication

When prescribing esomeprazole for the eradication of *Helicobacter pylori*, possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolized via CYP3A4 such as cisapride. levels before starting PPI treatment and periodically during treatment.

Gastrointestinal infections

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

Absorption of vitamin B12

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

Hypomagnesaemia

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

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium

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 recognized 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.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered. See section 4.5.

Serious cutaneous adverse reactions (SCARs)

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms.

Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional

medical care/close monitoring should be provided as needed.

Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS. Sucrose

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

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Sodium content

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

Domepridone

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.

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 (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 patient 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 patient should consult their physician.

Patient should be advised to promptly report any cardiac symptoms.

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.

Excipients

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Esomeprazole

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section 4.4) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3).

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

Methotrexate

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

Tacrolimus

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

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the

plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy.

Diazepam

Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC by 15% and 41%, respectively.

Cilostazol

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

Cisapride

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Warfarin

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

Clopidogrel

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

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

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

Investigated medicinal products with no clinically relevant interaction
Amoxicillin and quinidine

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

Naproxen or rofecoxib

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

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280%. A

dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

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

Paediatric population

Interaction studies have only been performed in adults.

Domepridone

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 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 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 (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.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e : • protease inhibitors

• systemic azole antifungals

• some macrolides (erythromycin, clarithromycin and telithromycin)

(see section 4.3).

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

(see section 4.3)

Concomitant use of 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 contraindicated 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

Esomeprazole

Pregnancy

Clinical data on exposed pregnancies with Esomeprazole are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Breast-feeding

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

Fertility

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

Domepridone

Pregnancy

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

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 women. Caution should be exercised in case of QTc prolongation risk factor in breast-fed infants.

4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported (see section 4.8). If affected patients should not drive or use machines.

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

4.8 Undesirable effects

Esomeprazole

Summary of the safety profile

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 drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and

post-marketing. None was found to be dose-related. The reactions are classified according to Headache, abdominal pain, diarrhoea, and nausea are among those 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
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section 4.4); 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
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
Hepatobiliary disorders	Not known	Microscopic colitis
	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
Skin and subcutaneous tissue disorders	Very rare	Hepatic failure, encephalopathy in patients with preexisting liver disease
	Uncommon	Dermatitis, pruitus, rash, urticaria
	Rare	Alopecia, photosensitivity

	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)
	Not known	Subacute cutaneous lupus erythematosus (see section
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Domepridone

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 (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 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 disorder			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	Urticarial 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National reporting system Website: https://pv.pharmacyboardkenya.org

4.9 Overdose

Esomeprazole

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

Domepridone

Symptoms

Symptoms of overdosage 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.

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 and reduces gastric acid secretion through a specific targeted mechanism

of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the *R*- and *S*-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects

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

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

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

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

One week of treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10%

respectively) were randomized to receive Esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral Esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the Esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the Esomeprazole treated versus the placebo treated group 7.7% vs 13.6%.

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

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

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

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

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

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

Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

Domepridone

Pharmacotherapeutic Group: Propulsives, ATC code: A03F A03

Mechanism of action

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 oesophageal 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 effect 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 7.5msec (95 % CI: 0.6 to 14.4), respectively.

Clinical study in infants and children 12 years of age and younger
A multicentre, double-blind, 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 episodes during the first 48 hours after the first treatment administration (see section 4.2).

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 dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

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

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Elimination

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination

half-life is about 1.3 hours after repeated once daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Linearity/non-linearity

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

Special patient populations

Poor metabolisers

Approximately 2.9 ±1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. These findings have no implications for the posology of esomeprazole.

*Hepatic impairment*The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction.

Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal impairment

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

esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly

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

Paediatric population

Adolescents 12-18 years:

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

Domepridone

Absorption

Domperidone is rapidly absorbed after oral administration with peak plasma concentrations occurring at approximately 1 hr 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 gastrointestinal 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 21ng/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.

Hepatic impairment

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 (see section 4.3).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance<30 ml/min/1.73m2) 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 severity of the impairment, and the dose may need to be reduced.

Paediatric population

No pharmacokinetic data are available in the Pharmacokinetic properties.

5.3 Preclinical safety data

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.

Domepridone

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 proarrhythmic 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 45.4ng/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

Maize Starch Purified

Talc Magnesium Stearate

Sodium Starch Glycolate

Hydrophobic colloidal anhydrous silica

Dibasic calcium phosphate

Povidone (PVPK-30)

Methyl Hydroxybenzoate

Propyl Hydroxybenzoate

Opadry white 85 G 68918

Acrl-eze orange 93053668

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

Protect from light and moisture.

6.5 Nature and contents of container

Each Alu-Alu strip contains 10 tablets & such 10 strips are pack in carton with package insert (100 Tablets)..

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorization holder and manufacturing site address

Marketing authorization holder:

Next Wave (India)

Address: SCO No. 313, Second Floor, Sector 29, Gurugram, 122009, Haryana, India.

Manufacturing site address:

Next Wave (India)

Address: SCO No. 313, Second Floor, Sector 29, Gurugram, 122009, Haryana, India

8. Marketing authorization number

CTD9435

9. Date of first registration

02/08/2023

10. Date of revision of the text:

17/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable

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