SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Esofag-D

1.1 Strength

40 mg & 30 mg

1.2 Pharmaceutical form

Hard gelatin Capsules '1' size Blue/Clear transparent Micro Printed containing white & orange colored pellets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:
Esomeprazole Magnesium Trihydrate BP Equivalent to Esomeprazole BP 40 mg
(as enteric coated pellets)
Domperidone BP 30 mg
(as sustained release pellets)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin Capsules '1' size Blue/Clear transparent Micro Printed containing white & orange colored pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

1 capsule once daily 15 minutes before breakfast or as prescribed.

4.3 Method of administration

For oral use.

4.4 Contraindications

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation

Esomeprazole should not be used concomitantly with nelfinavir

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

- 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
- in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure
- co-administration with QT-prolonging drugs
- co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

4.5 Special warnings and precautions for use

Esomeprazole

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

Long term use

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

On demand treatment

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

Helicobacter pylori eradication

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

Gastrointestinal infections

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

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 levels before starting PPI treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other 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.

Sub-acute 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 Nexium. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

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

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

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

Domperidone

Use in infants: Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

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. Such patients on prolonged therapy should be reviewed regularly.

Cardiovascular effects: Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and children.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic 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.

4.6 Paediatric population

None stated

4.7 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 and concomitant administration with esomeprazole and nelfinavir is contraindicated.

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_{τ} 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.

Warfarin

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

Clopidogrel

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

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

of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.
Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction

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_{τ} 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.

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 the following substances is contraindicated

QTc-prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquindine, 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 antihistaminic (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)
- Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e. protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin)

Concomitant use of the following substances is not recommended

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

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 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 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.

4.8 Additional information on special populations

None stated

4.9 Paediatric population

Interaction studies have only been performed in adults.

4.10 Fertility, Pregnancy and lactation

4.10.1 Women of childbearing potential / Contraception in males and females

None stated.

4.10.2 Pregnancy

Esomeprazole

Clinical data on exposed pregnancies with Nexium are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects. 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.

Domperidone

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

4.10.3 Breast-feeding

Esomeprazole

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.

Domperidone

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.

4.10.4 Fertility

Esomeprazole

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

4.11 Effects on ability to drive and use machines

Esomeprazole and Domperidone has no or negligible influence on the ability to drive and use machines. However, adverse reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or use machines.

4.12 Undesirable effects

Esomeprazole

Summary of the safety profile

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

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 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; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalemia.
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
	Not known	Microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
	Not known	Sub acute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported

		concomitantly.
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Domperidone

Tabulated list of adverse reactions

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 (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 gastro paresis 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 can not 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	Agitation

		Anxiety	Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsade de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticaria Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhea 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 gastro paresis, 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.

Paediatric population Extrapyramidal disorder occurs primarily in neonates and infants

Other central nervous system-related effects of convulsion and agitation also are primarily reported in infants and children.

4.13 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 utilized.

Domperidone

Symptoms: Overdose has been reported primarily in infants and children. Symptoms of over dosage 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, gastric lavage as well as the administration of activated charcoal, may be useful. 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: Peptic ulcer and gastro-oesophageal reflux disease(GORD).

ATC code for Esomeprazole: A02BC05, ATC code for Domperidone : A03FA03

Mechanism of action

Esomeprazole

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar Pharmacodynamic activity.

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

Domperidone

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 (gastro kinetic) 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.

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 catalyses 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 concentration (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

Domperidone

Absorption: In fasting subjects, domperidone is rapidly absorbed after oral administration with peak plasma concentrations at 30 to 60 minutes. 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 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.

5.3 Preclinical safety data

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.

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 rally 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:

Esomeprazole enteric coated pellets, Domperidone sustained release pellets, HEG Capsules shells of size '1'.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 Months.

6.4 Special precautions for storage:

Store below 30°C. Keep out from the reach of children

6.5 Nature and contents of container:

Alu Alu strip pack of 3 x 10's capsules

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

INDIA

8. MARKETING AUTHORISATION NUMBER

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9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

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10. DATE OF REVISION OF THE TEXT

May 2024

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable

13. DOCUMENT REVISION HISTORY

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