ESOMAC-D Capsules (Esomeprazole magnesium + Domperidone)
For the use of a Registered Medical Practitioner only

Qualitative And Quantitative Composition

ESOMAC D 20 Capsules
Each hard gelatin capsule contains:
Esomeprazole Magnesium Trihydrate IP equivalent to
Esomeprazole ........................... 20 mg
(as enteric coated pellets)
Colour: Titanium Dioxide IP
Domperidone IP ........................... 30 mg
(as sustained-release pellets)
Colours: Sunset Yellow Supra & Sunset Yellow Lake
Colours used in capsule shells: Titanium Dioxide IP, Carmoisine, Brilliant Blue, Sunset Yellow, Ponceau 4R

ESOMAC D 40 Capsules
Each hard gelatin capsule contains:
Esomeprazole Magnesium Trihydrate IP equivalent to
Esomeprazole ........................... 40 mg
(as enteric coated pellets)
Colour: Titanium Dioxide IP
Domperidone IP ........................... 30 mg
(as sustained-release pellets)
Colours: Sunset Yellow Supra & Sunset Yellow Lake
Colours used in capsule shells: Titanium Dioxide IP, Carmoisine, Brilliant Blue, Sunset Yellow, Ponceau 4R

Dosage Forms And Strengths

Capsules for oral use:
ESOMAC D 20: 20 mg esomeprazole + 30 mg domperidone
ESOMAC D 40: 40 mg esomeprazole + 30 mg domperidone

Clinical Particulars

- **Therapeutic Indications**

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

- **Posology and Method of Administration**

Dosage
ESOMAC D capsule should be taken once daily at least 1 hour before meals.

**Method of Administration**
The capsules should be swallowed whole with liquid. The capsules should not be opened or chewed or crushed.

It is recommended to take ESOMAC D before meals.

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

**Special Populations**

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

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

**Hepatic impairment**
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded (see section Pharmacokinetic Properties).

Domperidone is contraindicated in moderate or severe hepatic impairment. Dose modification in mild hepatic impairment is however not needed.

**Geriatric population**
Dose adjustment is not required in the elderly.

**Pediatric Population**
Safety and effectiveness of ESOMAC D in pediatric patients have not been established

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**Contraindications**

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

Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria (see section Undesirable Effects).

Esomeprazole should not be used concomitantly with nelfinavir.

**Domperidone**
Domperidone is contraindicated in the following situations:
- Known hypersensitivity to domperidone
- Prolactin-releasing pituitary tumour (prolactinoma).
- when stimulation of the gastric motility could be harmful e.g. in patients with 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, at the exception of apomorphine.
- co-administration with potent CYP3A4 inhibitors.
**Special Warnings and Precautions for Use**

**Esomeprazole**

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

**Long Term Use**

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

**On Demand Treatment**

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

**Gastrointestinal Infections**

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

**Absorption of Vitamin B12**

Esomeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy (e.g. longer than 3 years).

**Hypomagnesaemia**

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

**Risk of Fracture**

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

**Subacute Cutaneous Lupus Erythematosus (SCLE)**

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to
years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving esomeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

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

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

Clostridium difficile-Associated Diarrhea
Published observational studies suggest that PPI therapy like esomeprazole may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve (see section Undesirable Effects).

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole, refer to Warnings and Precautions section of the corresponding prescribing information.

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

Combination with other medicines
Co-administration of esomeprazole with atazanavir is not recommended (see section Drug Interactions). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded. Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section Drug Interactions). 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 Drug Interactions).
Drugs which induce CYP2C19 or CYP3A4 (such as St. John’s Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole with St. John’s Wort or rifampin. Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section Pharmacodynamic Properties).
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.

Domperidone
Cardiovascular effects
Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section Undesirable Effects).
Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section Undesirable Effects). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.
Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.
Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.
Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.
Patients should be advised to promptly report any cardiac symptoms.
Use with apomorphine
Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the coadministration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.
Renal impairment
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.

Drug Interactions
Esomeprazole
Effects of esomeprazole on the pharmacokinetics of other medicinal products

Protease inhibitors
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, $C_{\text{max}}$ and $C_{\text{min}}$). 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 once daily) 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 once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, $C_{\text{max}}$, and $C_{\text{min}}$ by 36–39 % and mean AUC, $C_{\text{max}}$ and $C_{\text{min}}$ 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 Special Warnings and Precautions for Use) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section Contraindications).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily 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 omeprazole 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, atazanavir, iron salts, mycophenolate mofetil (MMF), 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 medicinal product monitoring of digoxin should then be reinforced.

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

*Medicinal products metabolised by CYP2C19*

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is
combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine,
clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased, and
a dose reduction could be needed.

This should be considered especially when prescribing esomeprazole for on-demand therapy.

*Diazepam*

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

*Phenytoin*

Concomitant oral administration of 40 mg esomeprazole and phenytoin 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) $C_{\text{max}}$ and $AUC_{\tau}$ 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 $C_{\text{max}}$ 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 oral administration of 40 mg esomeprazole and cisapride 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 oral 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 of oral esomeprazole, 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
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 or 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 oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCτ by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

**Medicinal products which induce CYP2C19 and/or CYP3A4**
Medicinal products 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. Avoid concomitant use of St. John's Wort or rifampin with esomeprazole.

**Pediatric population**
Interaction studies have only been performed in adults.

**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, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphenamid, methadone)
(see section Contraindications).
• 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
• systemicazole antifungals
• some macrolides (erythromycin, clarithromycin, telithromycin)
(see section Contraindications).

**Concomitant use of the following substances is not recommended**
Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.
(see section Contraindications)

**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's CYP3A4 mediated first pass metabolism by these drugs.
With the combination of oral domperidone 10 mg four times daily and ketoconazole 200 mg 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 10 mg four times daily and oral erythromycin 500 mg 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 10 mg 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 (200 mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

### Use in Special Population

#### Esomeprazole

**Pregnant Women**
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 foetotoxiqueffect.
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 esomeprazole 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 Animal Toxicology or Pharmacology).

**Lactating Women**
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.

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

**Geriatric Use**
Of the total number of patients who received esomeprazole in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age. No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Domperidone**

**Pregnant Women**
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 Animal Toxicology or Pharmacology). Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

**Lactating Women**
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.

**Effects on Ability to Drive and Use Machines**

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

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

**Undesirable Effects**

**Esomeprazole**

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

*Tabulated list of adverse reactions*
The following adverse medicinal product reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Rare</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Agranulocytosis, pancytopenia</td>
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<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock</td>
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<tr>
<td></td>
<td>Not known</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Peripheral oedema</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hypomagnesaemia (see section Special Warnings and Precautions for Use); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.</td>
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<tr>
<td>Psychiatric disorders</td>
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<td>Insomnia</td>
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<td></td>
<td>Rare</td>
<td>Agitation, confusion, depression</td>
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<td></td>
<td>Very rare</td>
<td>Aggression, hallucinations</td>
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<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
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<tr>
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<td>Uncommon</td>
<td>Dizziness, paraesthesia, somnolence</td>
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<td></td>
<td>Rare</td>
<td>Taste disturbance</td>
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</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Rare</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Stomatitis, gastrointestinal candidiasis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Microscopic colitis, pancreatitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Increased liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hepatitis with or without jaundice</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hepatic failure, encephalopathy in patients with pre-existing liver disease</td>
</tr>
</tbody>
</table>
### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dermatitis, pruritus, rash, urticaria</td>
</tr>
<tr>
<td>Rare</td>
<td>Alopecia, photosensitivity</td>
</tr>
<tr>
<td>Very rare</td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)</td>
</tr>
<tr>
<td>Not known</td>
<td>Subacute cutaneous lupus erythematosus (see section Special Warnings and Precautions for Use), hyperhidrosis</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Fracture of the hip, wrist, or spine (see section Special Warnings and Precautions for Use)</td>
</tr>
<tr>
<td>Rare</td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Muscular weakness</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Interstitial nephritis: in some patients, renal failure has been reported concomitantly</td>
</tr>
<tr>
<td>Not known</td>
<td>Acute kidney injury</td>
</tr>
</tbody>
</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Gynaecomastia</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Malaise, increased sweating</td>
</tr>
</tbody>
</table>

### Pediatrics

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

**Domperidone**

**Tabulated list of adverse reactions**

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

The following terms and frequencies are applied:

very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), Where frequency cannot be estimated from clinical trials data, it is recorded as “Not known”.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
</tr>
<tr>
<td></td>
<td>Common Uncommon Not known</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction (including anaphylactic shock)</td>
</tr>
</tbody>
</table>
### Psychiatric disorders
- Loss of libido
- Anxiety
- Agitation
- Nervousness

### Nervous system disorders
- Somnolence
- Headache
- Convulsion
- Extrapyramidal disorder

### Eye disorders
- Oculogyric crisis

### Cardiac disorders (see section Special Warnings and Precautions for Use)
- Ventricular arrhythmias
- Sudden cardiac death
- QTc prolongation
- Torsade de Pointes

### Gastrointestinal disorders
- Dry mouth
- Diarrhoea

### Skin and subcutaneous tissue disorder
- Rash
- Pruritus
- Urticaria
- Angioedema

### Renal and urinary disorders
- Urinary retention

### Reproductive system and breast disorders
- Galactorrhoea
- Breast pain
- Breast tenderness
- Gynaecomastia
- Amenorrhoea

### General disorders and administration site conditions
- Asthenia

### Investigations
- Liver function test abnormal
- Blood prolactin increased

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

**Reporting of suspected adverse reactions**

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. If your patient experiences any side-effects, write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side-effects, you can help provide more information on the safety of this product.

**Overdose**

**Esomeprazole**

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole. No specific antidote is known.

Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.
Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.

**Domperidone**

**Symptoms**
Symptoms of 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, 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.

**Pharmacological Properties**

**Esomeprazole**

**Mechanism of Action**
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.

**Pharmacodynamic Properties**
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 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours respectively, over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively 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 4 weeks, and in 93% after 8 weeks of oral treatment.

One week’s treatment with esomeprazole 20 mg twice daily 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 randomised, 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 randomised to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic
haemostasis, 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 was 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 oral treatment with antisecretory medicinal products, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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

**Clinical efficacy**

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

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

**Pediatric population**

No relevant data is available for esomeprazole in pediatric population.

**Pharmacokinetic Properties**

**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 medicinal product is found in urine.

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

**Special patient populations**

**Poor metabolisers**
Approximately 2.9 ±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

**Gender**
Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. These findings have no implications for the posology of esomeprazole.

**Hepatic impairment**
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

**Renal impairment**
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

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

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

**Pharmacodynamic Properties**

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

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

**Pharmacokinetic properties**

**Absorption**

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The $C_{\text{max}}$ and $AUC$ values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

**Distribution**

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

**Metabolism**

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome
P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

**Excretion**

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

**Special patient populations**

**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 Contraindications).

**Renal impairment**

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

**Paediatric population**

No pharmacokinetic data are available in the paediatric population.

**Nonclinical Properties**

**Animal Toxicology or Pharmacology**

**Esomeprazole**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

**Domperidone**

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered 3 times a day. Safety margins for prolongation of action potential duration in in vitro
experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45-fold. Safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- to 45-fold. In in vivo models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

### Description

Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. (Initial U.S. approval of esomeprazole magnesium: 2001). Its molecular formula is \((C_{17}H_{18}N_3O_3S)_2\text{Mg} \times 3\text{H}_2O\) with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.

The structural formula is:

![Esomeprazole Structural Formula](image)

Domperidone is a derivative of benzimidazole that possesses both pro-kinetic and anti-emetic properties due to its inhibitory action at dopamine D2-receptors.

### Pharmaceutical Properties

- **Incompatibilities**
  
  Not applicable.

- **Shelf-life**
  
  As on the pack.

- **Packaging Information**
  
  ESOMAC D Capsules 20 mg ....... Strip pack of 10 capsules
  ESOMAC D Capsules 40 mg ....... Strip pack of 10 capsules

- **Storage and Handling Instructions**
  
  Store below 25°C. Protect from light and moisture.
  Keep out of reach of children.
A. What is ESOMAC D and what is it used for?
ESOMAC D contains medicines called esomeprazole and domperidone. Esomeprazole belongs to a group of medicines called proton pump inhibitors. They work by reducing the amount of acid that your stomach produces. Domperidone belongs to a group of medicines called dopamine antagonists. ESOMAC D is used for the treatment of adult patients with gastroesophageal reflux disease (GERD) not responding to esomeprazole alone.
Gastroesophageal reflux disease (GERD) is a condition where acid from the stomach escapes into the food pipe (the tube which connects your throat to your stomach) causing pain, inflammation, and heartburn.

Children and adolescents aged 1-18 years
Safety and effectiveness of ESOMAC D have not been established in pediatric patients.

B. What you need to know before you take ESOMAC D?
DO not take ESOMAC D:
• If you are allergic to esomeprazole or domperidone or any of the other ingredients of this medicine. Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
• If you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, omeprazole).
• If you are taking a medicine containing nelfinavir (used to treat HIV infection).
• If you have a tumour of the pituitary gland (prolactinoma)
• If you have a blockage or tear in your intestines
• If you have black, tarry bowel motions (stools) or notice blood in your bowel motions. This could be a sign of bleeding in the stomach or intestines.
• If you have a moderate or severe liver disease.
• If your ECG (electrocardiogram) shows a heart problem called “prolonged QT corrected interval”.
• If you have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure).
• If you have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.
• If you are taking certain medicines (see “Other medicines and ESOMAC D”)
You must not take ESOMAC D if any of the above apply to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

Warnings and precautions
Talk to your doctor or nurse before you are given ESOMAC D if:
• You have severe liver problems.
• You have severe kidney problems.
• You have ever had a skin reaction after treatment with a medicine similar to esomeprazole that reduces stomach acid.
• You are due to have a specific blood test (Chromogranin A).
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking ESOMAC D. Do this even if they have applied in the past.
Esomeprazole may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you take esomeprazole or after you are given it, talk to your doctor straight away:
• You lose a lot of weight for no reason and have problems swallowing.
• You get stomach pain or indigestion.
• You begin to vomit food or blood.
• You pass black stools (blood-stained faeces).

If you have been prescribed esomeprazole “on demand” you should contact your doctor if your symptoms continue or change in character.

Taking a proton pump inhibitor like esomeprazole, especially over a period of more than one year, may slightly increase your risk of fracture in the hip, wrist, or spine. Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis).

If you get a rash on your skin, especially in areas exposed to the sun tell your doctor as soon as you can, as you may need to stop your treatment with ESOMAC D. Remember to also mention any other ill effects like pain in your joints.

Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day. The risk also increases when domperidone is given together with some drugs. Tell your doctor or pharmacist if you are taking drugs to treat infection (fungal infections or bacterial infection) and/or if you have heart problems or AIDS/HIV (see “Other medicines and ESOMAC D”).

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older and a body weight of 35kg or more.

While taking ESOMAC D, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with domperidone should be stopped.

Other medicines and ESOMAC D

Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines that you buy without a prescription. This is because ESOMAC D can affect the way some medicines work, and some medicines can have an effect on ESOMAC D.

You must not be given ESOMAC D if you are taking a medicine containing nelfinavir (used to treat HIV infection).

Tell your doctor or nurse if you are taking any of the following medicines:

• Protease inhibitors like atazanavir (used to treat HIV infection).
• Clopidogrel (used to prevent blood clots).
• Ketoconazole, itraconazole, fluconazole, or voriconazole (used to treat infections caused by a fungus).
• Erlotinib (used to treat cancer).
• Citalopram, imipramine or clomipramine (used to treat depression).
• Diazepam (used to treat anxiety, relax muscles or in epilepsy).
• Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop having ESOMAC D.
• Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop having ESOMAC D.
• Cilostazol (used to treat intermittent claudication – a pain in your legs when you walk which is caused by an insufficient blood supply).
• Cisapride, dolasetron, prucalopride (used for gastro-intestinal disorders including indigestion and heartburn).
• Digoxin (used for heart problems).
• Methotrexate (a chemotherapy medicine used in high doses to treat cancer) – if you are taking a high dose of methotrexate, your doctor may temporarily stop your ESOMAC D treatment.
• Tacrolimus (organ transplantation).
• Rifampicin (used for treatment of tuberculosis).
• St. John’s wort (*Hypericum perforatum*) (used to treat depression).
• Erythromycin, clarithromycin, telithromycin, moxifloxacin, pentamidine (antibiotics to treat bacterial infections).
• Amiodarone, dronedarone, quinidine, disopyramide, dofetilide, sotalol, diltiazem, verapamil (used to treat heart problems or high blood pressure)
• Haloperidol, pimozide, sertindole (for treating psychoses)
• Citalopram, escitalopram (to treat depression)
• Mequitazine, mizolastine (for treating allergy)
• Halofantrine (for malaria)
• Toremifene, vandetanib, vincamine (for treating cancer)

*ESOMAC D with food and drink*

ESOMAC D should be taken at least 1 hour before meals.

*Pregnancy, breast-feeding and fertility*

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine. Your doctor will decide whether you can take ESOMAC D during this time.

It is not known if esomeprazole passes into breast milk. Small amounts of domperidone have been detected in breast-milk. Domperidone may cause unwanted side effects affecting the heart in a breast-fed baby. Therefore, you should not be given ESOMAC D if you are breastfeeding.

*Driving and using machines*

Esomeprazole is not likely to affect you being able to drive or use any tools or machines. Domperidone does not affect your ability to drive or use machines. However, side effects such as dizziness and blurred vision may uncommonly occur. If affected, you should not drive or use machines.

*C. How to take ESOMAC D?*

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

• If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
• If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

*How much to take*

• Your doctor will tell you how many capsules to take and how long to take them for.

The usual dose is one capsule once daily.

*Taking this medicine*

• You should take your capsules at least one hour before taking a meal.
• Swallow your capsules whole with a drink of water. Do not open or chew or crush the capsules.

*Elderly*

Dose adjustment is not required in the elderly.

*People with kidney problems*

Your doctor may tell you to take a lower dose or to take the medicine less often.

*If you take more ESOMAC D than you should*

• If you take more ESOMAC D than prescribed by your doctor, talk to your doctor or pharmacist straight away. Take the carton and any capsules left with you. This is so the doctors know what you have taken.
In the event of overdose, symptomatic treatment could be implemented. An ECG monitoring could be undertaken, because of the possibility of a heart problem called prolonged QT interval.

The signs of taking more than you should include feeling sleepy, confused, uncontrolled movements which include unusual eye movements, unusual movements of the tongue or abnormal posture (such as a twisted neck).

If you forget to take ESOMAC D

- If you forget to take ESOMAC D, take it as soon as you remember.
- However, if it is almost time for the next dose, wait until that is due and then continue as normal.
- Do not take a double dose to make up for a forgotten dose.

D. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following serious side effects, stop taking ESOMAC D and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be ‘Stevens-Johnson syndrome’ or ‘toxic epidermal necrolysis’.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare and may affect up to 1 in 1,000 people.

Additionally, stop taking ESOMAC D and see your doctor or go to a hospital straightaway if:
- You have swelling of the hands, feet, ankles, face, lips or throat which may cause difficulty in swallowing or breathing. You could also notice an itchy, lumpy rash (hives) or nettle rash (urticaria). This may mean you are having an allergic reaction to domperidone.
- You have any uncontrolled movements. These include irregular eye movements, unusual movements of the tongue, and abnormal posture such as a twisted neck, trembling and muscle stiffness. This is more likely to happen in children. These symptoms should stop once you stop taking ESOMAC D.
- You have a very fast or unusual heartbeat. This could be a sign of a life-threatening heart problem.
- You have a fit (seizure).

Other side effects include:

Common (may affect up to 1 in 10 people)
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).
- Benign polyps in the stomach.

Uncommon (may affect up to 1 in 100 people)
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as “pins and needles”, feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Fracture of the hip, wrist or spine (if esomeprazole is used in high doses and over long duration).
- Lowering of sexual drive (libido) in men
- Feeling anxious
• Feeling drowsy
• Headaches
• Diarrhoea
• Unusual production of breast milk in men and women
• Painful or tender breasts
• A general feeling of weakness

**Rare (may affect up to 1 in 1,000 people)**
• Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
• Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
• Feeling agitated, confused or depressed.
• Eyesight problems such as blurred vision.
• Taste changes.
• Suddenly feeling wheezy or short of breath (bronchospasm).
• An inflammation of the inside of the mouth.
• An infection called “thrush” which can affect the gut and is caused by a fungus.
• Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
• Hair loss (alopecia).
• Skin rash on exposure to sunshine.
• Joint pains (arthritis) or muscle pains (myalgia).
• Generally feeling unwell and lacking energy.
• Increased sweating.

**Very rare (may affect up to 1 in 10,000 people)**
• Changes in blood count including agranulocytosis (lack of white blood cells)
• Aggression.
• Seeing, feeling or hearing things that are not there (hallucinations).
• Severe liver problems leading to liver failure and inflammation of the brain.
• Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
• Muscle weakness.
• Severe kidney problems.
• Enlarged breasts in men.

**Not known (frequency cannot be estimated from the available data)**
• If you are on esomeprazole for more than three months it is possible that the levels of magnesium in your blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate. If you get any of these symptoms, please tell your doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium.
• Inflammation in the gut (leading to diarrhea).
• Rash, possibly with pain in the joints.
• Inflammation of the pancreas (pancreatitis)
• Systemic lupus erythematosus
• Excessive sweating (hyperhidrosis)
• Kidney damage (acute kidney injury)
• Disorders of the cardiovascular system: heart rhythm disorders (rapid or irregular heart beat) have
been reported; if this happens, you should stop the treatment immediately. Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day.

Feeling agitated or irritable
Feeling more nervous than usual
Abnormal eye movements
Inability to urinate
Breast enlargement in men
In women, menstrual periods may be irregular or stop
A blood test shows changes in the way your liver is working.

Esomeprazole may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a severely reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medication at this time.

Some patients who have used domperidone for conditions and dosages requiring longer term medical supervision have experienced the following unwanted effects: Restlessness; swollen or enlarged breasts, unusual discharge from breasts, irregular menstrual periods in women, difficulty breastfeeding, depression, hypersensitivity.

Side effects such as feeling drowsy, nervous, agitated or irritable or having a fit are more likely to happen in children.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse write to drugsafety@cipla.com. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side-effects, you can help provide more information on the safety of this product.

E. How to store ESOMAC D?
• Keep this medicine out of reach of children.
• Store below 25°C. Protect from light and moisture.
• Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
• Store this medicine in the original package (blister).
• Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

F. Contents of the pack and other information?
What ESOMAC D contains
ESOMAC D capsules contain the active substances esomeprazole magnesium trihydrate and domperidone. ESOMAC D capsules come in two strengths containing 20 mg or 40 mg of esomeprazole (as magnesium trihydrate). Both strengths contain 30 mg domperidone.

Details Of Manufacturer

Mfd. By M/s Innova Captab Ltd.,
1281/1, Hilltop Industrial Estate,
Details Of Permission Or License Number With Date

MNB/16/970 dated 10/03/2017

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24/04/2020

ESOMAC-D Capsules

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