**For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only**

## NEXPRO RD

1. **Generic Name**

   Esomeprazole Magnesium and Domperidone Sustained Release Capsules

2. **Qualitative and quantitative**

   **composition NEXPRO RD 20**

   Each hard gelatin capsule contains:

   Esomeprazole Magnesium Trihydrate I.P.

   Equivalent to Esomeprazole……..20 mg

   (as enteric coated tablet)

   Domperidone Maleate I.P.

   Equivalent to Domperidone…….30 mg

   (as uncoated bilayered sustained release tablet)

   Colours: Red Oxide of Iron and Titanium Dioxide I.P.

   Approved colours used in hard gelatin capsule shell.

   The excipients used are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

   **NEXPRO RD 40**

   Each hard gelatin capsule contains:

   Esomeprazole Magnesium Trihydrate I.P.

   Equivalent to Esomeprazole……40 mg

   (as enteric coated tablet)

   Domperidone Maleate I.P.

   Equivalent to Domperidone ……30 mg

   (as uncoated bilayered sustained release tablet)

   Colours: Red Oxide of Iron and Titanium Dioxide I.P.

   Approved colours used in hard gelatin capsule shell.

   The excipients used are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

## 3. Dosage form and strength

Dosage form: Capsules

Strength: Esomeprazole 20 mg and Domperidone 30 mg

Esomeprazole 40 mg and Domperidone 30 mg

## 4. Clinical particulars

### 4.1 Therapeutic indication

It is indicated for the treatment of adult patients with gastroesophagal reflux disease (GERD) not responding to esomeprazole alone.

### 4.2 Posology and method of administration Posology

**Adults**

Gastroesophageal Reflux Disease (GERD)

- Treatment of erosive reflux esophagitis

The recommended dose is one capsule per day. An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed esophagitis to prevent relapse The recommended dose is one capsule per day.

- symptomatic treatment of gastroesophageal reflux disease (GERD)

The recommended dose is one capsule per day in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using single capsule once daily.

**Special Populations**

*Renal impairment*

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

*Hepatic impairment*

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, dose shall be adjusted as recommended by physician.

*Elderly*

Dose adjustment is not required in the elderly.

**Method of administration**

The capsules should be swallowed whole with half a glass of water. The capsules must not be chewed, crushed or opened.

### 4.3 Contraindications

**Esomeprazole**

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

excipients. Esomeprazole should not be used concomitantly with nelfinavir.

**Domperidone**

Domperidone is contraindicated in the following situations:

• Known hypersensitivity to domperidone or any of the excipients

• Prolactin-releasing pituitary tumour (prolactinoma).

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

• In patients with moderate or severe hepatic impairment

• 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 (regardless of their QT prolonging effects).

## 4.4 Special warnings and precautions for use

**Esomeprazole**

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

*Long term use*

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

*On demand treatment*

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

*Helicobacter pylori eradication*

When prescribing esomeprazole for 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 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 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. 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. 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.

*Interference with laboratory tests*

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

**Domperidone**

*Cardiovascular effects*

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT

prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

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

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

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

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

Patients should be advised to promptly report any cardiac symptoms.

*Use with apomorphine*

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

*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.

## 4.5 Drugs interactions

**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, Cmax and Cmin). 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, Cmax and Cmin by 36–39 % and mean AUC, Cmax and Cmin 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) Cmax and AUC by 15% and 41%, respectively.

*Cilostazol*

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

*Cisapride*

In healthy volunteers, concomitant administration of 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 (t1/2) 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 by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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

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

**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, diphemanil, methadone)
• apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC.

*Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:*
• protease inhibitors
• systemic azole antifungals
• some macrolides (erythromycin, clarithromycin, 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's CYP3A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

## 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

**Esomeprazole**

**Pregnancy**

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.

**Breast-feeding**

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

**Fertility**

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

**Domperidone**
**Pregnancy**

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses. Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

**Breast-feeding**

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants

## 4.7 Effects on ability to drive and use machines

**Esomeprazole**

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

**Domperidone**

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

## 4.8 Undesirable effects

**Esomeprazole**

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 as below.

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 (see section 4.4); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia. |
| Psychiatric disorders | Uncommon | Insomnia |
| | Rare | Agitation, confusion, depression |
| | Very rare | Aggression, hallucinations |
| Nervous system disorders | Common | Headache |
| | Uncommon | Dizziness, paraesthesia, somnolence |
| | Rare | Taste disturbance |
| Eye disorders | Rare | Blurred vision |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Rare | Bronchospasm |
| Gastrointestinal disorders | Common | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign) |
| | Uncommon | Dry mouth |
| | Rare | Stomatitis, gastrointestinal candidiasis |
| | 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 | Subacute cutaneous lupus erythematosus (see section 4.4) |
| Musculoskeletal and connective tissue disorders | Uncommon | Fracture of the hip, wrist or spine (see section 4.4) |
| | Rare | Arthralgia, myalgia |
| | Very rare | Muscular weakness |
| Renal and urinary disorders | Very rare | Interstitial nephritis; in some patients renal failure has been reported concomitantly; acute kidney injury |
| 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 reported clinical trials and in postmarketing experience. The reported clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of domperidone (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

The following terms and frequencies are applied:

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

| **System Organ Class** | **Adverse Drug Reaction Frequency** | | |
|---|---|---|---|
| | **Common** | **Uncommon** | **Not known** |
| **Immune system disorders** | | | Anaphylactic reaction (including anaphylactic shock) |
| **Psychiatric disorders** | | Loss of libido<br>Anxiety | Agitation<br>Nervousness |
| **Nervous system disorders** | | Somnolence<br>Headache | Convulsion<br>Extrapyramidal disorder |
| **Eye disorders** | | | Oculogyric crisis |
| **Cardiac disorders (see section 4.4)** | | | Ventricular arrhythmias<br>Sudden cardiac death<br>QTc prolongation<br>Torsade de Pointes |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Dry mouth | Diarrhoea | |
| **Skin and subcutaneous tissue disorder** | | Rash<br>Pruritus | Urticaria<br>Angioedema |
| **Renal and urinary disorders** | | | Urinary retention |
| **Reproductive system and breast disorders** | | Galactorrhoea<br>Breast pain<br>Breast tenderness | Gynaecomastia<br>Amenorrhoea |
| **General disorders and administration site conditions** | | Asthenia | |
| **Investigations** | | | Liver function test abnormal<br>Blood prolactin increased |

In 45 reported 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 side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

## 4.9 Overdose

**Esomeprazole**

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

**Domperidone**

*Symptoms*

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

*Treatment*

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

# 5. Pharmacological properties

## 5.1 Mechanism of Action

### Esomeprazole

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. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40mg and leads to inhibition of gastric 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 adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

## 5.2 Pharmacodynamic properties

### Esomeprazole

Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors
ATC code: A02B C05

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

### Pharmacodynamic effects

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

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

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

Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

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

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

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

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

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

During long-term treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

**Clinical efficacy**

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

**Paediatric population**

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

**Domperidone**

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

**Pharmacodynamics effect**

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. 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.

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.

## 5.3 Pharmacokinetic properties

### Esomeprazole

### Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68%, respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

### Distribution

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

### Biotransformation

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

### Elimination

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers. Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about

1.3 hours after repeated once daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

*Linearity/non-linearity*

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

*Special patient populations*
*Poor metabolisers*

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

*Gender*

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

*Hepatic impairment*

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

*Renal impairment*

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

*Elderly*

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

*Paediatric population*

Adolescents 12-18 years:

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

**Domperidone**
**Absorption**

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

**Distribution**

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.

*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.

*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.

## 6. Nonclinical properties

### Esomeprazole

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

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

### Domperidone

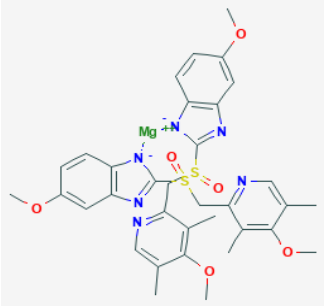
Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-fold, based on IC50 values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

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

## 7. Description

### Esomeprazole

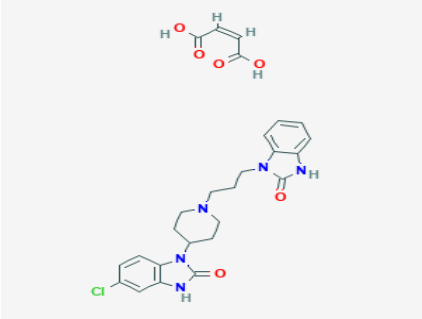
Esomeprazole is bis 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]benzimidazol-1-ide magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole. The molecular formula is $C_{34}H_{36}MgN_6O_6S_2$, and the molecular weight is 713.1 g/mol. The structural formula is:



Esomeprazole Magnesium Trihydrate is white to off-white powder which is soluble in N,N-dimethyl formamide.

### Domperidone

Domperidone Maleate is 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one-maleate with molecular formula as $C_{22}H_{24}ClN_5O_2$,$C_4H_4O_4$ and molecular weight as 452g/mol with the structural formula as below:



### NEXPRO RD 20

Esomeprazole Magnesium and Domperidone Sustained Release Capsules are size “1” purple/purple hard gelatin capsules printed with “Nexpro RD 20” and Torrent logo (Square emblem only) on the shell of capsules containing one brick red coloured, round shaped, biconvex, enteric coated, plain tablet and one brown red-peach coloured, capsule shaped uncoated bilayered tablet. The excipients used are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

**NEXPRO RD 40**

Esomeprazole Magnesium and Domperidone Sustained Release Capsules are size "0" violet/violet hard gelatin capsules printed with "Nexpro RD 40" and Torrent logo (Square emblem only) on the shell of capsules containing brick red coloured, capsule shaped, biconvex, enteric coated, plain tablet and one brown red-peach coloured, capsule shaped uncoated bilayered tablet. The excipients used are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

## 8. Pharmaceutical particulars

### 8.1 Incompatibilities

None stated

### 8.2 Shelf-life

Do not use later than the date of expiry.

### 8.3 Packaging information

NEXPRO RD is packed in strips of 10 capsules.

### 8.4 Storage and handing instructions

Store below 25°C, protected from light and moisture. Keep out of reach of children.

## 9. Patient counselling information

**Package leaflet: Information for the user**

**NEXPRO RD**

**Esomeprazole Magnesium And Domperidone Sustained Release Capsules**

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet?**

9.5.How to store NEXPRO RD

9.6. Contents of the pack and other information

## 9.1 What NEXPRO RD is and what it is used for

NEXPRO RD contains the active substance Esomeprazole Magnesium and Domperidone.

NEXPRO RD is used for treatment of adult patients with gastroesophagal reflux disease (GERD) not responding to esomeprazole alone.

Reflux is the backflow of acid from the stomach into the gullet ("foodpipe"), which may become inflamed and painful. This may cause you symptoms such as a painful burning sensation in the chest rising up to the throat (heartburn) and a sour taste in the mouth (acid regurgitation). You may experience relief from your acid reflux and heartburn symptoms after just one day of treatment with NEXPRO RD, but this medicine is not meant to bring immediate relief. It may be necessary to take the tablets for 2–3 consecutive days to relieve the symptoms. You must talk to a doctor if you do not feel better or if you feel worse after 2 weeks.

## 9.2 What you need to know before you take NEXPRO RD

Do not take NEXPRO RD:

– if you are allergic to Esomeprazole Magnesium, Domperidone or to any of the other ingredients of this medicine.

– if you are taking HIV protease inhibitors such as atazanivir, nelfinavir (for the treatment of HIV-infection).

– Co-administration with QT-prolonging drugs, at the exception of apomorphine

– Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

Warnings and precautions

Talk to your doctor before taking NEXPRO RD:

– if you have been treated for heartburn or indigestion continuously for 4 or more weeks – if you are over 55 years old and taking non-prescription indigestion treatment on a daily basis

– if you are over 55 years old with any new or recently changed reflux symptoms

– if you have previously had a gastric ulcer or stomach surgery

– if you have liver problems or jaundice (yellowing of skin or eyes)

– if you regularly see your doctor for serious complaints or conditions

– if you are due to have an endoscopy or a breath test called a C-urea test.

– if you have ever had a skin reaction after treatment with a medicine similar to NEXPRO RD that reduces stomach acid.

– if you are due to have a specific blood test (Chromogranin A) – if you are taking HIV protease inhibitors such as atazanivir, nelfinavir (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advice.

Do not take this product for longer than 4 weeks without consulting your doctor. If your reflux symptoms (heartburn or acid regurgitation) persist for longer than 2 weeks, consult your doctor who will decide about the need for long-term intake of this medicinal product.

If you take NEXPRO RD for longer periods, this may cause additional risks, such as: – reduced absorption of Vitamin B12, and Vitamin B12 deficiency if you already have low body stores of Vitamin B12.

– fracture of your hip, wrist or spine, especially if you already suffer from osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis).

– falling magnesium levels in your blood (potential symptoms: fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate). Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. You should talk to your doctor if you have been using this product for more than 4 weeks. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium.

Tell your doctor immediately, before or after taking this medicine, if you notice any of the following symptoms, which could be a sign of another, more serious, disease:

– an unintentional loss of weight (not related to a diet or an exercise programme)

– vomiting, particularly if repeated

– vomiting blood; this may appear as dark coffee grounds in your vomit

– you notice blood in your stools; which may be black or tarry in appearance

– difficulty in swallowing or pain when swallowing – you look pale and feel weak (anaemia)

– chest pain

– stomach pain

– severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea.

– 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 NEXPRO RD. Remember to also mention any other ill-effects like pain in your joints.

– if signs or symptoms occur that may be associated with cardiac arrhythmia

Your doctor may decide that you need some tests.

If you are due to have a blood test, tell your doctor that you are taking this medicine.

You should not take it as a preventive measure.

If you have been suffering from repetitive heartburn or indigestion symptoms for some time, remember to see your doctor regularly.

**Children and adolescents**

NEXPRO RD should not be used by children and adolescents under 18 years of age due to a lack of safety information in this younger age group.

**Other medicines and NEXPRO RD**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

NEXPRO RD may stop certain other medicines from working properly. Especially medicines containing one of the following active substances:

– HIV protease inhibitors such as atazanavir, nelfinavir (for the treatment of HIV-infection). You must not use NEXPRO RD if you are taking HIV protease inhibitors. See 'Do not take NEXPRO RD'.

– disopyramide, hydroquinidine, quinidine, amiodarone and dronedarone (QT prolongation medications).

– warfarin (used to thin blood and prevent clots). You may need further blood tests.

– methotrexate (used to treat rheumatoid arthritis, psoriasis, and cancer)

– if you are taking methotrexate your doctor may temporarily stop your NEXPRO RD treatment because esomeprazole can increase levels of methotrexate in the blood.

Do not take NEXPRO RD with other medicines which limit the amount of acid produced in your stomach, such as another proton pump inhibitor (pantoprazole, lansoprazole or rabeprazole) or an H2 antagonist (e.g. ranitidine, famotidine). However, you may take NEXPRO RD with antacids (e.g. magaldrate, alginic acid, sodium bicarbonate, aluminium hydroxide, magnesium carbonate, or combinations thereof), if needed.

**Pregnancy and breast-feeding and fertility**

You should not take this medicine if you are pregnant or while breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

NEXPRO RD has a low likelihood of affecting your ability to drive or use machines. If you experience side effects like dizziness or disturbed vision, you should not drive or use machines.

## 9.3 How to take NEXPRO RD

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet a day. Method of administration: Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

For the treatment of Gastro-esophageal reflux diseases (GERD). The usual dose is one tablet a day. You should take this medicine for at least 2–3 consecutive days. Stop taking NEXPRO RD when you are completely symptom-free. If you have no symptom-relief after taking this medicine for 2 weeks continuously, consult your doctor. Do not take NEXPRO RD tablets for more than 4 weeks without consulting your doctor.

**If you take more NEXPRO RD than you should**

Tell your doctor or pharmacist if you have taken more than the recommended dose. If possible take your medicine and this leaflet with you.

**If you forget to take NEXPRO RD**

Do not take a double dose to make up for the forgotten dose. Take your next, normal dose, the next day, at your usual time.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

## 9.4 Possible side effects

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

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects. Stop taking this medicine straight away, but take this leaflet and/or the tablets with you.

– Serious allergic reactions (rare: may affect up to 1 in 1,000 people): Hypersensitivity reactions, so-called anaphylactic reactions, anaphylactic shock and angioedema. Typical symptoms are: swelling of the face, lips, mouth, tongue and/or throat, which may cause difficulty in swallowing or breathing, hives (nettle rash), severe dizziness with very fast heartbeat and heavy sweating.

– Serious skin reactions (frequency not known: frequency cannot be estimated from the available data): rash with swelling, blistering or peeling of the skin, losing skin and bleeding around eyes, nose, mouth or genitals and rapid deterioration of your general health, or rash when exposed to the sun.

– Other serious reactions (frequency not known): yellowing of the skin and eyes (due to severe liver damage), or kidney problems such as painful urination and lower back pain with fever.

– 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.

– You have a very fast or unusual heartbeat. This could be a sign of a life-threatening heart problem. You have a fit (seizure). You notice 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.

*Other side effects include*:

– *Common (may affect up to 1 in 10 people)*

• Headache.
• Effects on your stomach or gut: diarrhoea, stomach ache, constipation, wind (flatulence).
• Feeling sick (nausea) or being sick (vomiting).
• Benign growths (polyps) in the stomach.

– *Uncommon (may affect up to 1 in 100 people)*

• Swelling of the feet and ankles.
• Disturbed sleep (insomnia), feeling sleepy.
• Dizziness, tingling feelings such as “pins and needles”.
• Spinning feeling (vertigo).
• Dry mouth.
• Increased liver enzymes shown in blood tests that check how the liver is working.

• Skin rash, lumpy rash (hives), and itchy skin.

– *Rare (may affect up to 1 in 1,000 people)*

• Blood problems such as a reduced number of white blood 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.
• Taste changes.
• Eyesight problems such as blurred vision.
• Suddenly feeling wheezy, or short of breath (bronchospasm).
• An inflammation on the inside of the mouth.
• An infection called "thrush" which can affect the gut and is caused by a fungus.
• Hair loss (alopecia).
• Skin rash on exposure to sunshine.
• Joint pain (arthralgia), or muscle pain (myalgia).
• Generally feeling unwell and lacking energy.
• Increased sweating.

– *Very rare (may affect up to 1 in 10,000 people)*

• Low numbers of red blood cells, white blood cells, and platelets (a condition called pancytopenia).
• Aggression.
• Seeing, feeling, or hearing things that are not there (hallucinations).
• Severe liver problems leading to liver failure and inflammation of the brain.
• Muscle weakness.
• Severe kidney problems.
• Enlarged breasts in men.

– *Not known (frequency cannot be estimated from the available data)*

• Low levels of magnesium in the bloods. This may cause weakness, being sick (vomiting), cramps, tremor, and changes in heart rhythm (arrhythmias). If you have very low levels of magnesium, you may also have low levels of calcium and/or potassium in your blood.
• Inflammation of the gut (leading to diarrhoea).
• Rash, possibly with pain in the joints.
• 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. Feeling agitated or irritable

**Domperidone**

Other side effects include:

Common (may affect up to 1 in 10 people):

• Dry mouth

Uncommon (may affect up to 1 in 100 people):

• Lowering of sexual drive (libido) in men

• Feeling anxious

• Feeling drowsy

• Headaches

• Diarrhoea

• Itchy skin. You may also have a rash

• Unusual production of breast milk in men and women

• Painful or tender breasts

• A general feeling of weakness

Not known (Frequency cannot be estimated from the available data):



• 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. Domperidone should be used at the lowest effective dose.

• 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.

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.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

**9.5 How to store NEXPRO RD**

Store below 25°C, protected from light and moisture. Keep out of reach of children.

**9.6 Contents of the pack and other information**

**What NEXPRO RD contains**

**The active substances in NEXPRO RD are Esomeprazole Magnesium and Domperidone.**

The excipients used in **NEXPRO RD 20** are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

The excipients used in **NEXPRO RD 40** are Mannitol, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Crospovidone, Talc, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Talc, Lactose, Polyvinyl Pyrrolidone, Colloidal Silicon Dioxide and Red Oxide of Iron.

**10. Details of manufacturer**

Ravenbhel Biotech
EPIP, SIDCO, Kartholi, Bari-Brahmana, Jammu – 181133

**11. Details of permission or licence number with date**

Mfg. Lic. No. : JK/01/11-12/192 issued on 04.09.2015

**12. Date of revision**

**Feb /2022**

**MARKETED BY**

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

**IN/NEXPRO RD/20/40mg,30mg/Feb 22/04/PI**