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

Nexpro IV

1. Generic Name

Esomeprazole Sodium Powder for Injection

2. Qualitative and quantitative composition

Each carton contains:
A) Each vial contains:
Esomeprazole Sodium Ph.Eur.
Equivalent to Esomeprazole 40 mg
B) Each ampule contains:
Sodium Chloride Injection I.P.
0.9 % w/v q.s to 5 ml

The other excipients are Di sodium EDTA, sodium hydroxide.

3. Dosage form and strength

Dosage Form: Powder for Injection
Strength: 40 mg

4. Clinical particulars

4.1 Therapeutic indication

For Gastroesophageal Reflux Disease (GERD) in patients with esophagitis and severe symptoms of reflux as an alternative to oral therapy when oral intake is no appropriate.

4.2 Posology and method of administration

Patients who cannot take oral medication may be treated parenterally with 20–40 mg once daily. Patients with reflux esophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily.

Injection:

40 mg dose: 5 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose: 2.5 ml or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

10 mg dose: 1.25 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

Infusion: The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

Children and adolescents aged 1-18 years

Gastric antisecretory treatment when the oral route is not possible: Patients who cannot take oral medication may be treated parenterally once daily as directed by

physician.

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

GERD: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg Esomeprazole I.V. should not be exceeded.

Bleeding ulcers: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg Esomeprazole for infusion, a continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient.

Elderly

Dose adjustment is not required in the elderly

Method of administration

For instructions on reconstitution of the medicinal product before administration.

4.3 Contraindications

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

Esomeprazole should not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

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 Nexpro IV may alleviate symptoms and delay diagnosis.

Gastrointestinal infections

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

Absorption of vitamin B12

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

Hypomagnesaemia

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

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 Nexpro IV. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

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

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products 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.

4.5 Drugs interactions

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 CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C and C). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C

and C by 36-39% and mean AUC, C and C 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 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 administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

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

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C

and AUC by 15% and 41%, respectively.

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C 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 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) 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 CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCt 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. Long-term treatment is indicated in adults and adolescents (12 years and older, see section 4.1).

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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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. The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. 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 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, diarrnoea, flatulence ausea/vomiting, fundic gland polyps (benign)
	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 d isorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours) (see section 5.3). Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. 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

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.

5. Pharmacological properties

5.1 Mechanism of Action

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

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitor
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

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 effect is similar irrespective of whether esomeprazole is administered orally or intravenously.

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

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours and 11-13 hours, respectively, over 24 hours in healthy subjects.

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.

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 NEXPRO IV 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 NEXPRO IV for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXPRO IV treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the NEXPRO IV 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.

Paediatric population

In a placebo-controlled study (98 patients aged 1-11 months) efficacy and safety in patients with signs and symptoms of GERD were evaluated. Esomeprazole 1 mg/kg

once daily was given orally for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening.

In a placebo-controlled study (52 patients aged < 1 month) efficacy and safety in patients with symptoms of GERD were evaluated. Esomeprazole 0.5 mg/kg once daily was given orally for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GERD.

Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg esomeprazole in < 1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-oesophageal pH < 4.

The safety profile appeared to be similar to that seen in adults.

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.

5.3 Pharmacokinetic properties

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

Total exposure (AUC) increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/l. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/l. A smaller increase (of approx 30%) can be seen in total exposure after intravenous

administration compared to oral administration. There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23.5 hours.

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%. Similar differences have been seen for intravenous administration of esomeprazole. 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. Similar differences have been observed for intravenous administration of esomeprazole. 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 total exposure of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in GERD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. 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

In a randomised, open-label, multi-national, repeated dose study, esomeprazole was given as a once-daily 3-minute injection over four days. The study included a total of 59 paediatric patients 0 to 18 years old of which 50 patients (7 children in the age group 1 to 5 years) completed the study and were evaluated for the pharmacokinetics of esomeprazole.

The table below describes the systemic exposure to esomeprazole following the intravenous administration as a 3-minute injection in paediatric patients and adult healthy subjects. The values in the table are geometric means (range). The 20 mg dose for adults was given as a 30-minute infusion. The C was measured 5 minutes post-dose in all paediatric groups and 7 minutes post-dose in adults on the 40 mg

dose, and after stop of infusion in adults on the 20 mg dose.

Age group	**Dose group**	**AUC (µmol*h/l)**	**$C_{ss,max}$ (µmol/l)**
0-1 month*	0.5 mg/kg (n=6)	7.5 (4.5-20.5)	3.7 (2.7-5.8)
1-11 months*	1.0 mg/kg (n=6)	10.5 (4.5-22.2)	8.7 (4.5-14.0)
1-5 years	10 mg (n=7)	7.9 (2.9-16.6)	9.4 (4.4-17.2)
6-11 years	10 mg (n=8)	6.9 (3.5-10.9)	5.6 (3.1-13.2)
	20 mg (n=8)	14.4 (7.2-42.3)	8.8 (3.4-29.4)
	20 mg (n=6)**	10.1 (7.2-13.7)	8.1 (3.4-29.4)
12-17 years	20 mg (n=6)	8.1 (4.7-15.9)	7.1 (4.8-9.0)
	40 mg (n=8)	17.6 (13.1-19.8)	10.5 (7.8-14.2)
Adults	20 mg (n=22)	5.1 (1.5-11.8)	3.9 (1.5-6.7)
	40 mg (n=41)	12.6 (4.8-21.7)	8.5 (5.4-17.9)

* A patient in the age group 0 up to 1 month was defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age was the sum of the gestational age and the age after birth in complete weeks. A patient in the age group 1 to 11 months had a corrected age of ≥44 complete weeks.

** Two patients excluded, 1 most likely a CYP2C19 poor metaboliser and 1 on concomitant treatment with a CYP3A4 inhibitor.

Model based predictions indicate that $C_{ss,max}$ following intravenous administration of esomeprazole as a 10 minute, 20 minute and 30 minute infusions will be reduced by on average 37% to 49%, 54% to 66% and 61% to 72%, respectively, across all age and dose groups compared to when the dose is administered as a 3 minute injection.

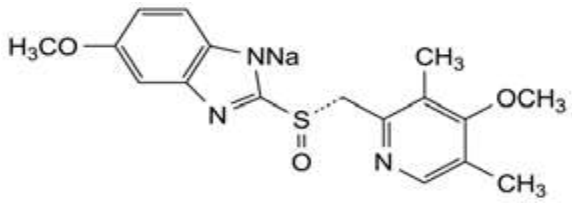
6. Nonclinical properties

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:

Oral carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects 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. In the non-clinical program for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection was noted.

7. Description

Esomeprazole Magnesium Trihydrate is 5-methoxy-2-{ (S)[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}- 1H-benzimidazole magnesium trihydrate. having molecular formula of C17H18N3NaO3S molecular weight is 367.4 the chemical structure is:



Esomeprazole is a white or almost white, amorphous or crystalline powder, slightly hygroscopic. Which is freely soluble in water and ethanol (96 percent), soluble in propylene glycol, very slightly soluble in methylene chloride.

Product Description:
Nexpro IV: White to off white powder or cake

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

Available in Sterile single dose vial.

8.4 Storage and handing instructions

DO NOT STORE ABOVE 30 ºC, PROTECT FROM LIGHT.

9. Patient counselling information

Nexpro IV

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?

9.1 What NEXPRO IV is and what it is used for

Nexpro IV contains a medicine called esomeprazole. This belongs to a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces.

Nexpro IV is used for the short-term treatment of certain conditions, when you are unable to have treatment by mouth. It is used to treat the following conditions:

Adults

• ‘Gastroesophageal reflux disease’ (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.

Children and adolescents aged 1-18 years

• ‘Gastroesophageal reflux disease’ (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.

9.2 What you need to know before you take NEXPRO IV

You must not be given Nexpro IV:

• If you are allergic to esomeprazole or any of the other ingredients of this medicine (listed in section 6).

• 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).

You must not be given NEXPRO IV 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 NEXPRO IV 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 NEXPRO IV that reduces stomach acid.

• You are due to have a specific blood test (Chromogranin A).

Nexpro IV may hide the symptoms of other diseases. **Therefore, if any of the following happen to you before you are given NEXPRO IV 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).

Taking a proton pump inhibitor like NEXPRO IV, 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 NEXPRO IV. Remember to also mention any other ill effects like pain in your joints.

Other medicines and Nexpro IV

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 NEXPRO IV can affect the way some medicines work and some medicines can have an effect on NEXPRO IV.

You must not be given NEXPRO IV 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:

• Atazanavir (used to treat HIV infection).

• Clopidogrel (used to prevent blood clots).
• Ketoconazole, itraconazole 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 NEXPRO IV.
• Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop having NEXPRO IV.
• Cilostazol (used to treat intermittent claudication – a pain in your legs when you walk which is caused by an insufficient blood supply).
• Cisapride (used for 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 NEXPRO IV treatment.
• Tacrolimus (organ transplantation).
• Rifampicin (used for treatment of tuberculosis).
• St. John's wort (Hypericum perforatum) (used to treat depression).

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 NEXPRO IV during this time.
It is not known if NEXPRO IV passes into breast milk. Therefore, you should not be given NEXPRO IV if you are breastfeeding.

Driving and using machines

Nexpro IV is not likely to affect you being able to drive or use any tools or machines. However, side effects such as dizziness and blurred vision may uncommonly occur (see section 4). If affected, you should not drive or use machines.

9.3 How to take NEXPRO IV

Nexpro IV can be given to children and adolescents aged 1-18 years and adults, including the elderly.

Being given Nexpro IV

Use in adults

• Nexpro IV will be given to you by your doctor who will decide how much you need.
• The recommended dose is 20 mg or 40 mg once a day.
• If you have severe liver problems, the maximum dose is 20 mg a day (GERD).
• The medicine will be given to you as an injection or infusion into one of your veins. This will last for up to 30 minutes.
• The recommended dose for prevention of re-bleeding of gastric or duodenal ulcer, is 80 mg administered as intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/hr given over 3 days. If you have severe liver problems, a continuous infusion of 4 mg/hr given over 3 days may be sufficient.

Use in children and adolescents

• Nexpro IV will be given by your doctor who will decide how much you need.
• For children 1-11 years, the recommended dose is 10 or 20 mg given once a day.
• For children 12-18 years, the recommended dose is 20 or 40 mg given once a day.

• The medicine will be given as an injection or infusion into a vein. This will last up to 30 minutes.

If you are given more Nexpro IV than you should

If you think you have been given too much Nexpro IV, talk to your doctor straight away**.**

9.4 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 NEXPRO IV 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.

Other side effects include:

Common (<u>may affect up to 1 in 10 people</u>)

• Headache.

• Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).

• Feeling sick (nausea) or being sick (vomiting).

• Injection site reaction.

• Benign polyps in the stomach.

Uncommon (<u>may affect up to 1 in 100 people</u>)

• Swelling of the feet and ankles.

• Disturbed sleep (insomnia).

• Dizziness, tingling feelings such as "pins and needles", feeling sleepy.

• Spinning feeling (vertigo).

• Eyesight problems such as blurred vision.

• 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 NEXPRO IV is used in high doses and over long duration).

Rare (<u>may affect up to 1 in 1,000 people</u>)

• 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.

• 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 (arthralgia) 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 NEXPRO IV 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 diarrhoea).
• Rash, possibly with pain in the joints.

NEXPRO IV 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.

Reporting of side effects

If you get any side effects, talk to your doctor. 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.

9.5 How to store

DO NOT STORE ABOVE 30 ºC, PROTECT FROM LIGHT.

9.6 Contents of the pack and other information

Each carton contains:
A) Each vial contains:
Esomeprazole Sodium Ph.Eur.
Equivalent to Esomeprazole 40 mg
B) Each ampule contains:
Sodium Chloride Injection I.P.
0.9 % w/v q.s to 5 ml
Direction: To be reconstituted with sodium chloride injection I.P. 0.9 % w/v (5 ml) (Provided in this pack) immediately before use.

The other excipients are Di sodium EDTA, sodium hydroxide.

10. Details of manufacturer

TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.
At: G-17/1, MIDC,
Tarapur Industrial area,
Bolsar, Dist. Thane-401 506.

11. Details of permission or licence number with date

KD-1832 A issued on 24.05.2019

12. Date of revision

May/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
IN/NEXPRO IV/40 mg/May-20/06/PI