

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

NEXPRO IT

1. Generic Name

Enteric coated Esomeprazole 40 mg and Itopride Hydrochloride sustained release 150 mg capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Esomeprazole Magnesium Trihydrate I.P

equivalent to Esomeprazole 40 mg

(As enteric coated pellets)

Itopride Hydrochloride I.P..... 150 mg

(As sustained release pellets)

Colours: Ferric Oxide USP-NF (Yellow), Titanium Dioxide I.P.

Excipients..... q.s.

Approved colours used in capsule shell

Excipients used are Light magnesium carbonate, Maize Starch, Anhydrous disodium hydrogen phosphate, Hypromellose, Purified talc, MethacryAcid & EthylAcryCoDis, Sodium hydroxide, Titanium Dioxide, Macrogol, Colloidal Anhydrous Silica, Non pareil seeds, Povidone K, Ethyl cellulose, Triacetin.

3. Dosage form and strength

Dosage form: Hard gelatin capsule

Strength: Esomeprazole 40 mg and Itopride Hydrochloride 150 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of GERD not responding to Esomeprazole alone.

4.2 Posology and method of administration

Dose: As directed by Physician

4.3 Contraindications

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. Nexpro IT should not be used concomitantly with nelfinavir.

Nexpro IT must not be used in patients in whom increased gastrointestinal motility could be harmful, e.g. in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Esomeprazole magnesium Trihydrate

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 (see section 5.1).

Absorption of vitamin B12

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

Hypomagnesaemia

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

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

Risk of fracture

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

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

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

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

Sucrose

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

Interference with laboratory tests

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

Itopride hydrochloride

Itopride potentiates acetylcholine action and can induce side anticholinergic effects.

Data on long-term use are not available.

Paediatric Use

Safety of itopride in children under the age of 16 has not been established.

Geriatric Use

In general, appropriate caution should be exercised in the administration and monitoring of itopride hydrochloride in elderly patients reflecting the greater frequency of decreased hepatic, renal function, and of concomitant disease or other drug therapy.

4.5 Drugs interactions

Esomeprazole magnesium Trihydrate

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

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

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of

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

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

Methotrexate

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

Tacrolimus

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

Medicinal products with pH dependent absorption

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

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy.

Diazepam

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

Phenytoin

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

Voriconazole

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

Cilostazol

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

Cisapride

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

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.

Itopride hydrochloride

Metabolic interactions are not expected since itopride is primarily metabolized by flavine monooxygenase and not by CYP450. No changes in protein binding have been seen with coadministration of warfarin, diazepam, diclofenac sodium, ticlopidine hydrochloride, nifedipine, and nicardipine hydrochloride. Since itopride has gastrokinetic effects it could influence the absorption of concomitantly orally administered drugs. Particular caution should be taken with drugs with a narrow therapeutic index, sustained release or enteric-coated formulations. Anti-ulcer drugs like cimetidine, ranitidine, teprenone and cetraxate do not affect the prokinetic action of itopride. Anticholinergic may reduce the action of itopride.

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

Esomeprazole magnesium trihydrate

Pregnancy

Clinical data on exposed pregnancies with Esomeprazole 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 reported 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.

Reported 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 newborn/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.

Itopride hydrochloride

There are no adequate and well-controlled studies in pregnant women. Therefore, itopride hydrochloride should not be used during pregnancy unless the benefits outweigh the potential risks.

Labor and Delivery

There are no known effects of itopride hydrochloride on labor or delivery.

Breast-feeding

Because itopride is excreted in milk in rats, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Nexpro IT can affect patient's ability to drive and operate machinery. It should be taken into account that occasionally dizziness and fatigue may occur. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

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 $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1,000$ to $< 1/100$; rare $\geq 1/10,000$ 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

Itopride hydrochloride

According to a reported clinical trial report, clinical trials (Phase I – Phase III) itopride hydrochloride was well tolerated and no serious adverse reactions were reported. A total of 19 adverse drug reactions in 14 patients were reported out of 572 cases with an incidence of 2.4%. The majority of these **adverse** reactions occurring in more than one patient consisted of diarrhea in 4 cases (0.7%), headache in 2 cases (0.3%), and abdominal pain in 2 cases (0.3%). Abnormal laboratory findings observed in the trials include decreased WBC (leukocytopenia) in 4 cases (0.7%), increased prolactin in 2 cases (0.3%).

Post-marketing Experience and Ongoing Clinical Studies

The following adverse events have been reported in patients receiving itopride hydrochloride.

Blood and lymphatic system disorders

Leukopenia and thrombocytopenia.

Immune system disorders

Anaphylactoid reaction

Endocrine disorders

Increased prolactin level and gynecomastia.

Nervous system disorders

Dizziness, headache, and tremor.

Gastrointestinal disorders

Diarrhea, constipation, abdominal pain, increased saliva, and nausea.

Hepato-biliary disorders

Jaundice.

Skin and subcutaneous tissue disorders

Rash, redness, and itching.

Investigations

Increased AST (SGOT), increased ALT (SGPT), increased gamma-GTP, increased alkaline phosphatase, and increased bilirubin.

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 magnesium trihydrate

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.

Itopride hydrochloride

There have been no reported cases of overdose in humans. In case of excessive overdose the usual measures of gastric lavage and symptomatic therapy should be applied

5. Pharmacological properties

5.1 Mechanism of Action

Esomeprazole magnesium trihydrate

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.

Itopride hydrochloride

Itopride hydrochloride activates gastrointestinal propulsive motility due to its dopamine D2 antagonizing activity and acetylcholinesterase inhibitory activity. Itopride activates acetylcholine release and inhibits its degradation.

5.2 Pharmacodynamic properties

Esomeprazole magnesium trihydrate

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.

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.

In a randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomised to receive Esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72-hour period, all patients received open label 40 mg oral Esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the Esomeprazole treated group compared to 10.3% for the placebo group. At 30 days' post-treatment, the occurrence of rebleeding in the Esomeprazole treated versus the placebo treated group was 7.7% vs 13.6%.

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

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

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

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

Paediatric population

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

Itopride hydrochloride

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, propulsives; ATC code: A03FA07.

Itopride activates the gastrointestinal propulsive motility by dopamine D2 receptors antagonistic action and acetylcholine esterase inhibitory action. Itopride activates acetylcholine release and inhibits its degradation. In addition, itopride has an antiemetic action which is based on interaction with dopamine D2 receptors in chemoreceptor zone. This action was demonstrated by dose dependent inhibition of apomorphine induced vomiting in dogs. Itopride accelerates stomach emptying in humans. In animal studies in dogs with a single dose administration itopride supported stomach emptying. Itopride has high specific action in upper part of gastrointestinal tract. Itopride does not influence plasma concentrations of gastrin.

Itopride hydrochloride also has antiemetic action through interaction with D2 receptors located in the chemoreceptor trigger zone. This was demonstrated by dose dependent inhibition of apomorphine-induced vomiting in dogs. In conscious dogs, itopride hydrochloride activates propulsive gastric motility through dopamine D2-receptor antagonistic actions and dose-dependent inhibition of acetylcholinesterase. Itopride hydrochloride has been shown to accelerate gastric emptying in humans, dogs and rats. In single-dose studies in dogs, itopride hydrochloride was shown to promote gastric emptying. The action of itopride hydrochloride is highly specific for the upper gastrointestinal tract. Itopride hydrochloride does not affect serum gastrin levels

5.3 Pharmacokinetic properties

Esomeprazole magnesium trihydrate

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 $2.9 \pm 1.5\%$ 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 (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

Itopride Hydrochloride

Metabolism

Itopride undergoes extensive hepatic metabolism in humans. Three (3) metabolites have been identified, of which only one exerts minor activity without pharmacological relevance (approximately 2-3% of that of itopride). The primary metabolite in humans is the N-oxide, generated by oxidation of the tertiary amine N-dimethyl group. Itopride is metabolized by a flavin-dependent mono-oxygenase (FMO3). The abundance and efficiency of the human FMO-isozymes can be subject to genetic polymorphisms, which can lead to a rare autosomal recessive condition known as trimethylaminuria (fish odor syndrome). The half-life of itopride may therefore be longer in trimethylaminuria patients. In vivo pharmacokinetic studies on CYP-mediated reactions revealed that itopride showed neither inhibitory nor inductive effect on CYP2C19 and CYP2E1. CYP content and uridine diphosphate glucuronosyl transferase activity were not altered with the administration of itopride.

Excretion

Itopride hydrochloride and its metabolites are primarily excreted in the urine. The urinary excretions of itopride and its N-oxide were 3.7% and 75.4%, respectively, in healthy subjects after oral administration of a single therapeutic dose.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Esomeprazole magnesium trihydrate

Reported 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:

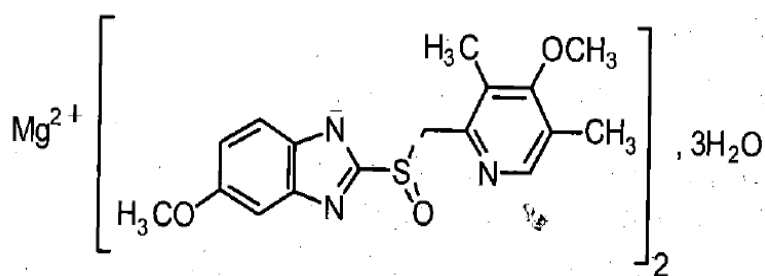
Reported carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment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

Itopride hydrochloride

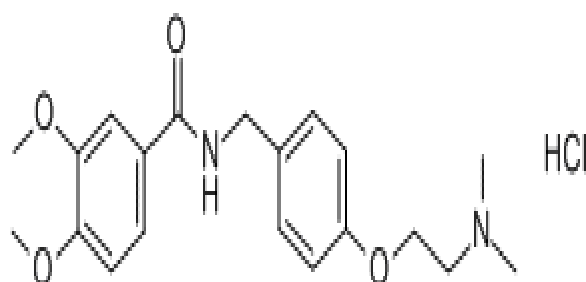
Reported preclinical safety data Oral single lethal dose was 2,000 mg/kg in mice and rats and approximately 600 mg/kg in dogs. Preclinical safety studies were carried out only with doses multiplicatively overrunning therapeutic human doses and found effect have only little importance for use of itopride in humans. In addition to it humans are less sensitive to hormonal effects observed in animals. High doses of itopride (30 mg/kg/day) caused hyperprolactinaemia and secondary reversible hyperplasia of uterine mucosa in rats. Nevertheless, this was not proved in dogs (dose up to 100 mg/kg/day) and monkeys (dose up to 300 mg/kg/day).

7. Description

Esomeprazole Magnesium Trihydrate is 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium trihydrate. The empirical formula of Esomeprazole Magnesium Trihydrate is $(C_{17}H_{18}N_3O_3S)_2, Mg.3H_2O$ and its molecular weight is 767.2 g/mol. The chemical structure of Esomeprazole Magnesium Trihydrate is:



Itopride Hydrochloride is *N*-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-3,4-dimethoxybenzamide;hydrochloride. The empirical formula of Itopride Hydrochloride is $C_{20}H_{27}ClN_2O_4$ and its molecular weight is 394.9 g/mol. The chemical structure of Itopride Hydrochloride is:



Nexpro IT is a mixture of yellow and white spherical to oval pellets filled in hard gelatin size '0' brown opaque cap and white opaque body unprinted capsule and strip packed. Excipients used are Light magnesium carbonate, Maize Starch, Anhydrous disodium hydrogen phosphate, Hypromellose, Purified talc, MethacryAcid & EthylAcryCoDis, Sodium hydroxide, Titanium Dioxide, Macrogol, Colloidal Anhydrous Silica, Non pareil seeds, Povidone K, Ethyl cellulose, Triacetin.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Nexpro IT is available in strip of 10 capsules.

8.4 Storage and handing instructions

Store below 25°C. Protect from light & moisture

Keep out of reach of children

9. Patient counselling information

NEXPRO IT

Enteric coated Esomeprazole 40 mg and Itopride Hydrochloride sustained release 150 mg 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?

9.1. What NEXPRO IT is and what it is used for

9.2. What you need to know before you take NEXPRO IT

9.3. How to take NEXPRO IT

9.4. Possible side effects

9.5. How to store NEXPRO IT

9.6. Contents of the pack and other information

9.1 What NEXPRO IT is and what it is used for

Nexpro IT is combination of Esomeprazole and Itopride. Esomeprazole belongs to a group of medicines called ‘proton pump inhibitors’. They work by reducing the amount of acid that your stomach produces. Itopride hydrochloride is an orally active gastroprokinetic agent. Itopride hydrochloride activates gastrointestinal propulsive motility.

Nexpro IT is used for the treatment of GERD not responding to Esomeprazole alone.

9.2 What you need to know before you take NEXPRO IT

Do not take NEXPRO IT:

- If you are allergic to esomeprazole, Itopride or any of the other ingredients of this medicine
- If you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, omeprazole).
- If you are taking a medicine containing nelfinavir (used to treat HIV infection).

If increase in movements of the digestive system, could be harmful, e.g. gastrointestinal bleeding, mechanical obstruction or perforation.

Do not take Nexpro IT if any of the above apply to you. If you are not sure, talk to your doctor before taking Nexpro IT.

Warnings and precautions

Talk to your doctor or pharmacist before taking Nexpro IT:

- If you have severe liver problems.
- If you have severe kidney problems.
- If you have ever had a skin reaction after treatment with a medicine similar to Nexpro IT that reduces stomach acid.
- If you are due to have a specific blood test (Chromogranin A).

In elderly patients

Special monitoring should be for elderly patients reflecting the greater frequency of decreased liver, kidney function, and of concomitant disease or other drug therapy

Nexpro IT may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you start taking Nexpro IT or while you are taking it, talk to your doctor straight away:

- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).

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

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

Children

Children below 12 years of age consult your doctor for because safety of product has may vary.

Other medicines and NEXPRO IT

Tell your doctor 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 IT can affect the way some medicines work and some medicines can have an effect on Nexpro IT.

Do not take Nexpro IT Tablets if you are taking a medicine containing nelfinavir (used to treat HIV infection).

Tell your doctor or pharmacist 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 taking Nexpro IT.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Nexpro IT.
- 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).
- Anticholinergic drugs
- 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 IT treatment.
- Tacrolimus (organ transplantation).
- Rifampicin (used for treatment of tuberculosis).
- St. John's wort (*Hypericum perforatum*) (used to treat depression).

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as Nexpro IT to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Nexpro IT with food and drink

You can take your tablets with food or on an empty stomach.

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 taking this medicine. Your doctor will decide whether you can take Nexpro IT during this time. It is not known if Nexpro IT passes into breast milk. Therefore, you should not take Nexpro IT if you are breastfeeding.

Driving and using machines

Nexpro IT 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 or rarely occur (see section 4). If affected, you should not drive or use machines.

9.3 How to take NEXPRO IT

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

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

How much to take

Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.

Dose: As directed by Physician

Taking this medicine

Swallow your tablets whole with a drink of water. Do not chew or crush the tablets. This is because the tablets contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you have trouble swallowing the tablets

If you have trouble swallowing the tablets:

- Put them into a glass of still (non-fizzy) water. Do not use any other liquids.
- Stir until the tablets break up (the mixture will not be clear). Then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
- To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.

If you cannot swallow at all, the tablet can be mixed with some water and put into a syringe. It can then be given to you through a tube directly into your stomach ('gastric tube'). Use in children under the age of 12 years Nexpro IT tablets are not recommended for children less than 12 years old

Elderly

Dose adjustment is not required in the elderly.

If you take more NEXPRO IT than you should

If you take more Nexpro IT than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take NEXPRO IT

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

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. If you notice any of the following serious side effects, stop taking Nexpro IT and contact a doctor immediately:

Esomeprazole

- 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 (may affect up to 1 in 10 people)**

- Dizziness, headache, and tremor.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence), increased, saliva, and nausea.
- Feeling sick (nausea) or being sick (vomiting).
- Benign polyps in the stomach
- Decrease Platelet count
- Increased milk production
- Excessive development of the male breasts
- Jaundice
- Rash, redness, and itching
- Liver dysfunctions

Uncommon (may affect up to 1 in 100 people)

- Swelling of the feet and ankles.

- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as “pins and needles”, feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Fracture of the hip, wrist or spine (if Nexpro IT is used in high doses and over long duration).

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

- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- 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 high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.

- Acute kidney injury
- Enlarged breasts in men.

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

- If you are on Nexpro IT 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.

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

Itopride hydrochloride

According to a reported clinical trial report, clinical trials (Phase I – Phase III) itopride hydrochloride was well tolerated and no serious adverse reactions were reported. A total of 19 adverse drug reactions in 14 patients were reported out of 572 cases with an incidence of 2.4%. The majority of these adverse reactions occurring in more than one patient consisted of diarrhea in 4 cases (0.7%), headache in 2 cases (0.3%), and abdominal pain in 2 cases (0.3%). Abnormal laboratory findings observed in the trials include decreased WBC (leukocytopenia) in 4 cases (0.7%), increased prolactin in 2 cases (0.3%).

Post-marketing Experience and Ongoing Clinical Studies

The following adverse events have been reported in patients receiving itopride hydrochloride.

Blood and lymphatic system disorders

Leukopenia and thrombocytopenia.

Immune system disorders

Anaphylactoid reaction

Endocrine disorders

Increased prolactin level and gynecomastia.

Nervous system disorders

Dizziness, headache, and tremor.

Gastrointestinal disorders

Diarrhea, constipation, abdominal pain, increased saliva, and nausea.

Hepato-biliary disorders

Jaundice.

Skin and subcutaneous tissue disorders

Rash, redness, and itching.

Investigations

Increased AST (SGOT), increased ALT (SGPT), increased gamma-GTP, increased alkaline phosphatase, and increased bilirubin.

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.

9.5 How to store NEXPRO IT

Store below 25°C. Protect from light & moisture

Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
- Store this medicine in the original package (blister) or keep the bottle tightly closed in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

9.6 Contents of the pack and other information

The active substance is Esomeprazole 40 mg and Itopride 150 mg

Excipients used are Light magnesium carbonate, Maize Starch, Anhydrous disodium hydrogen phosphate, Hypromellose, Purified talc, MethacryAcid & EthylAcryCoDis, Sodium hydroxide, Titanium Dioxide, Macrogol, Colloidal Anhydrous Silica, Non pareil seeds, Povidone K, Ethyl cellulose, Triacetin.

Nexpro IT is available in strip of 10 capsules

10. Details of manufacturer

Inventia Healthcare Limited.

F1-F1/1-F75/1, Additional Ambernath M.I.D.C,

Ambernath (East) -421506, Dist. Thane

11. Details of permission or licence number with date

Mfg. lic. No. KD-638 dated 19.10.2021

12. Date of revision

Not Applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/ NEXPRO IT 40,150mg/May-22/02/PI