PRODUCT NAME	:	Nexpro Tablets	**COUNTRY :** Malaysia	**LOCATION :** Chhatral	**Supersedes A/W No.:**						
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1	**REMARK :**							
DESIGN STYLE	:	Front/Back	**PANTONE SHADE NOS.:**	**SUBSTRATE :**							
CODE	:	xxxxxxxxx-5253	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**			
DIMENSIONS (MM)	:	180 x 340		Prepared By	**Pkg.Dev**						
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**						
DATE	:	04-06-2020		Approved By	**Quality**						

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

xxxxxxxx-5253

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

NEXPRO TABLETS 20 mg
NEXPRO TABLETS 40 mg

Esomeprazole Magnesium Gastro Resistant Tablets 20 mg & 40 mg

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

NEXPRO TABLETS 20 MG

Each gastro- resistant tablet contains
Esomeprazole magnesium equivalent to Esomeprazole ..... 20 mg
Colours: Red oxide of Iron and Titanium Dioxide

NEXPRO TABLETS 40 MG

Each gastro-resistant tablet contains
Esomeprazole magnesium equivalent to Esomeprazole ..... 40 mg
Colours: Red oxide of Iron and Titanium Dioxide

PRODUCT DESCRIPTION

Esomeprazole Tablets 20 mg are brick red colored, round shape, biconvex, film coated tablets, imprinted with “20” on one side with black ink and plain on other side.

Esomeprazole Tablets 40 mg are brick red colored, round shape, beveled edge, biconvex, film coated tablets, imprinted with “40” on one side with black ink and plain on other side.

DOSAGE FORM

Gastro resistant Tablets

PHARMACODYNAMICS

Pharmacodynamics

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.

Site and 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.

Effect on gastric acid secretion

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

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients.

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

Other effects related to acid inhibition

During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with esomeprazole.

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.

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.

Pharmacokinetic

Absorption and distribution

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. 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.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and excretion

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.

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. 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. 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.

Special patient populations

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

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

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.

Impaired organ function

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.

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.

Paediatric

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 drug concentration (tmax) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

INDICATION

Esomeprazole is indicated for the treatment of :

Gastro-Oesophageal Reflux Disease (GERD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GERD)

In combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* and

- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

Patients requiring continued NSAID therapy

Healing of gastric ulcers associated with NSAID therapy.

Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

RECOMMENDED DOSAGE AND MODE OF ADMINISTRATION

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coat may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested.

Adults and adolescents from the age of 12 years.

Gastro-Oesophageal Reflux Disease (GERD)

- <u>treatment of erosive reflux oesophagitis</u>

40 mg once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

- <u>long-term management of patients with healed oesophagitis to prevent relapse</u>

20 mg once daily.

- <u>symptomatic treatment of gastro-oesophageal reflux disease (GERD)</u>

20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

Adults

In combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* and

- <u>healing of Helicobacter pylori associated duodenal ulcer and</u>
- <u>prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.</u>

20 mg Esomeprazole with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy

Healing of gastric ulcers associated with NSAID therapy:

The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:

20 mg once daily.

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers.

40 mg once daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is Esomeprazole 40 mg twice daily. The dosage should then be individually adjusted and treatment continues as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 and 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice-daily.

Children below the age of 12 years

Esomeprazole should not be used in children younger than 12 years since no data is available.

Impaired renal function

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.

Impaired hepatic function

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

Elderly

Dose adjustment is not required in the elderly.

CONTRAINDICATIONS

- Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.
- Esomeprazole should not be used concomitantly with nelfinavir.

WARNINGS AND PRECAUTIONS

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.

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

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

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.

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.

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

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

<u>**Regular Surveillance**</u>

Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

<u>Subacute Cutaneous Lupus Erythematosus (SCLE)</u>

Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (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 Tablets. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

<u>**Hypomagnesaemia**</u>

Severe hypomagnesaemia has been reported in patients treated with PPI 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 PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

<u>**Fracture**</u>

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.

<u>**Clostridium Difficile Diarrhea**</u>

Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, Nexpro Tablets treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). 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.

INTERACTIONS WITH OTHER MEDICAMENTS

Effects of esomeprazole on the pharmacokinetics of other drugs

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

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. 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.

Drugs 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. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. 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. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC by 15% and 41%, respectively.

Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects of other drugs on the pharmacokinetics of esomeprazole

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. 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.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

For Esomeprazole, clinical data on exposed pregnancies are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal 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.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Esomeprazole should not be used during breast-feeding.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

The following adverse drug reactions have been identified for esomeprazole. None was found to be dose-related. The reactions are classified according to frequency (common>1/100, <1/10; uncommon>1/1000, <1/100; rare>1/10000, <1/1000; very rare <1/10000).

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

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
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis
Frequency '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)

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Rare: Malaise, increased sweating

<u>Subacute Cutaneous Lupus Erythematosus (SCLE)</u>
Skin and subcutaneous tissue disorders
Frequency 'not known': Subacute cutaneous lupus erythematosus

<u>Interstitial Nephritis</u>
Renal and urinary disorders: Interstitial nephritis

<u>Hypomagnesaemia</u>
Metabolism and nutritional disorders
Frequency "not known": hypomagnesaemia.

<u>Fracture</u>
Musculoskeletal disorders
Frequency “uncommon”: Fracture of the hip, wrist or spine.

<u>Clostridium Difficile Diarrhea</u>
Infections & infestations: Clostridium difficile associated diarrhea.

<u>Fundic Gland Polyps (Benign)</u>
Gastrointestinal disorders
Frequency "common": Fundic gland polyps (benign)

<u>Vitamin B12 Deficiency</u>
Metabolic/Nutritional: Vitamin B12 deficiency

Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280mg 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.

STORAGE CONDITIONS

Store below 30^{o}C.

PACKAGING AVAILABLE

Esomeprazole gastro resistant tablets are packed in alu alu Blister containing 7 tablets in each blister. Such blister strips are packed in box of 14’s and 28’s. Not all presentations or all pack sizes may be marketed.

DATE OF REVISION OF PACKAGE INSERT

04/06/2020

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.