PRODUCT NAME	:	Nexpro	**COUNTRY :** Philippines		**LOCATION :** Indrad	**Supersedes A/W No.:**
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1		**REMARK :**	
DESIGN STYLE	:	Front/Back	**PANTONE SHADE NOS.:**		**SUBSTRATE :**	
CODE	:	xxxxxxxx-5343		**Activities**	**Department**	**Name**	**Date**
DIMENSIONS (MM)	:	150 x 300		Prepared By	**Pkg.Dev**		
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**		
DATE	:	09-01-2018	■ Black	Approved By	**Quality**		

xxxxxxxxx-5343

ESOMEPRAZOLE

NEXPRO-20
NEXPRO-40

20 mg & 40 mg Enteric-Coated Tablet
Proton Pump Inhibitor

FORMULATION:
Each enteric-coated tablet contains:
Esomeprazole magnesium equivalent to
Esomeprazole ..... 20 mg and 40 mg

PRODUCT DESCRIPTION:
Esomeprazole (Nexpro-20) 20 mg Enteric-Coated Tablet is a brick red colored, round shape, biconvex, film coated tablet, imprinted with "20" on one side with black ink and plain on other side.
Esomeprazole (Nexpro-40) 40 mg Enteric-Coated Tablet is a brick red colored, round shape, biconvex, film coated tablet, imprinted with "40" on one side with black ink and plain on other side.

PHARMACODYNAMICS:
Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it is concentrated and converted to the active form in the acidic environment of the secretory canaliculi and inhibits the enzyme H+K+ ATPase the proton pump. This effect on the final step of the gastric secretion is dose- dependent and provides for effective inhibition of both basal and stimulated acid secretion.

Effects on Gastric acid secretion:
After oral dosing with esomeprazole 20mg and 40mg the onset of effects occurs within 1 hour. After repeated administration with 20mg esomeprazole once daily for 5 days, mean acid output after pentagastrin stimulation is decreased by 90% when measured 6-7 hours after dosing on day 5. After 5 days of oral dosing with 20mg and 40mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic gastro-esophageal reflux disease (GERD) patients.
The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76%, 54% and 24% respectively for esomeprazole 20mg. Corresponding proportions for esomeprazole 40mg were 97%, 92% and 56% respectively.
Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.
Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

Other effects related to acid inhibition:
During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion. During long-term treatment with antisecretory drugs gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

PHARMACOKINETICS:
Esomeprazole is rapidly absorbed after oral doses, with peak plasma levels occurring after about 1 to 2 hours. Bioavailability of esomeprazole increases with both dose and repeated administration to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolized in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolized by the cytochrome P450 isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme.
However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the feces.

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

Patients with renal impairment
No studies have been reported 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.

Patients with 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.

Pharmacogenetics
Approximately 1-2% of the population lack a functional CYP2CI9 enzyme and are called poor metabolizers. In these individuals, the metabolism of esomeprazole is probably mainly catalyzed by CYP3A4. It is reported that after repeated once-daily administration of 40mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%.

INDICATION:
Esomeprazole is indicated in the following conditions:

Gastro-esophageal Reflux Disease (GERD):
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastro-esophageal reflux disease (GERD)

Patients requiring continued NSAID therapy:
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy in patients at risk

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori:
- healing of Helicobacter pylori associated duodenal ulcer
- prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcer disease.

CONTRAINDICATIONS:
Hypersensitivity to Esomeprazole, substituted Benzimidazoles or any of the excipients of the product.

DOSAGE AND ADMINISTRATION:

Gastro-esophageal Reflux Disease (GERD):
- treatment of erosive reflux oesophagitis 40mg once daily for 4 weeks. An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.
- long-term management of patients with healed esophagitis to prevent relapse 20mg once daily.
- symptomatic treatment of gastro-esophageal reflux disease (GERD) 20mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on demand regimen, taking 20mg once daily, when needed.

Patients requiring continued NSAID therapy:
- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: 20 mg or 40mg once daily.

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori
- healing of Helicobacter pylori associated duodenal ulcer.
- prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcer disease. 20mg Esomeprazole with 1 g amoxicillin and 500mg clarithromycin, all twice daily for 7 days.

Children:
There is no experience with Esomeprazole in children.

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 daily dose of 20 mg Esomeprazole should be used.

Elderly:
Dose adjustment is not required in the elderly.

DIRECTIONS FOR USE:
The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.
The tablets can also be dispersed in half a glass of non- carbonated water. No other liquids should be used. 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.
For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube.

WARNINGS & 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 metabolized via CYP3A4 such as cisapride.
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. Esomeprazole dose should not exceed 20 mg and must be taken approximately 12 hours prior to atazanavir 300 mg with ritinavir 100 mg dose.

Effects on the ability to drive and use machines:
Esomeprazole is not likely to affect the ability to drive or use machines.

DRUG INTERACTIONS:
Interaction with other medicinal products and other forms of interaction:

Effects of esomeprazole on the pharmacokinetics of other drugs:
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.
Esomeprazole inhibits CYP2C19, the major Esomeprazole metabolizing enzyme. Concomitant administration of 30mg Esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance. Concomitant administration of 40mg Esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients.
Concomitant administration of 40 mg esomeprazole to warfarin treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, as with all patients receiving warfarin, monitoring is recommended during concomitant treatment with esomeprazole.
In healthy volunteers it was reported that, concomitant administration of 40mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t1/2) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.
Esomeprazole has no pharmacokinetic interaction with amoxicillin or quinidine.
Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

Effects of other drugs on the pharmacokinetics of esomeprazole:
Esomeprazole is metabolized by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500mg twice a day), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

PREGNANCY AND LACTATION:
Safety during pregnancy and lactation has not been established.

ADVERSE EFFECTS:
The following adverse drug reactions have been identified or suspected in the clinical trials program for esomeprazole and post-marketing. 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

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

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE & TREATMENT
A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. There have been no reports of overdose with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

STORAGE AND CONDITION:
Store at temperatures not exceeding 30°C. Protect from light and moisture.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Esomeprazole (Nexpro-20) 20 mg Enteric-Coated Tablet - Alu-Alu Blister pack of 10's (Box of 30's) - DR-XY41267

DATE OF FIRST AUTHORIZATION:
October 8, 2012
Esomeprazole (Nexpro-40) 40 mg Enteric-Coated Tablet - Alu-Alu Blister pack of 10's (Box of 30's) - DR-XY41252

DATE OF FIRST AUTHORIZATION:
September 19, 2012

DATE OF REVISION:
June 2016

Manufactured by :
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