xxxxxxxxx-8883

For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

NEXPRO

(Esomeprazole Magnesium Tablets, 20 mg and 40 mg)

COMPOSITION

Nexpro-20 : Each film coated tablet contains:
Esomeprazole Magnesium equivalent to
Esomeprazole (as enteric coated pellets)…..... 20mg.
Nexpro-40 : Each film coated tablet contains:
Esomeprazole Magnesium equivalent to
Esomeprazole (as enteric coated pellets)…..... 40mg.

DESCRIPTION

Esomeprazole is a proton pump inhibitor, the S-isomer of omeprazole. Esomeprazole suppresses gastric acid secretion by specific inhibition of the H^+ /K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of basal and stimulated gastric acid secretion.

The stability of Esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25^{o}C and about 8 hours at 37^{o}C.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

After oral administration of Esomeprazole magnesium, peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to Esomeprazole increases from 4.32 μmol.hr/L on day 1 to 11.2 μmol.hr/L on day 5 after 40mg once daily dosing.

The AUC after administration of a single 40mg dose of Esomeprazole is decreased by 33-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system.

Following administration of equimolar doses, the S-and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of Esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of Esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

The pharmacokinetics of Esomeprazole have not been studied in patients < 18 years of age.

Gender

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded.

Renal Insufficiency

The pharmacokinetics of Esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of Esomeprazole is excreted unchanged in urine.

Pharmacokinetics: Combination Therapy with Antimicrobials

The mean steady state AUC and C_{max} of Esomeprazole 40mg once daily, when given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000mg twice daily for 7 days, increased by 70% and 18%, respectively during triple combination therapy compared to treatment with Esomeprazole alone.

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

Nexpro is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8-week course of Nexpro may be considered.

Maintenance of Healing of Erosive Esophagitis

Nexpro is indicated to maintain symptom resolution and healing of erosive esophagitis.

Prevention of relapse of Esophagitis

Nexpro is indicated for prevenion of replase of esophagitis.

H. pylori Eradication to Reduce the Risk of Peptic Ulcer Recurrence

Triple Therapy (Esomeprazole plus amoxicillin and clarithromycin)

Nexpro, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and peptic ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*.

CONTRAINDICATIONS

Nexpro is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

PRECAUTIONS

General

Symptomatic response to therapy with Esomeprazole Magnesium does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which Esomeprazole Magnesium is an enantiomer.

Information for Patients

Patients should be informed of the following:

• Nexpro tablets should be taken at least one hour before meals.
• Antacids may be used while taking Nexpro.

DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that Esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that Esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin.

Esomeprazole may potentially interfere with CYP2C19, the major Esomeprazole-metabolizing enzyme. Coadministration of Esomeprazole 30mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Esomeprazole inhibits gastric acid secretion. Therefore, Esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts and digoxin).

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of Esomeprazole.

Combination Therapy with Clarithromycin

Co-administration of Esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of Esomeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with pimozide is contraindicated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole.

Gastric carcinoids seldom occurred in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test.

The potential effects of Esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Pregnancy Category B

Teratology studies performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) revealed no evidence of impaired fertility or harm to the fetus due to Esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

The excretion of Esomeprazole in milk has not been studied. Since Esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from Esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Esomeprazole Magnesium was well tolerated in both short and long-term clinical trials.

The most frequently occurring adverse events (≥1%) with Esomeprazole 20 mg and 40mg were headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.

Laboratory Events

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to Esomeprazole, were reported in ≤1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone; decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

DOSAGE AND ADMINISTRATION

Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis	20 mg or 40 mg Once Daily for 4 to 8 Weeks
Maintenance of Healing of Erosive Esophagitis	20 mg Once Daily
Prevention of relapse of esophagitis	20 mg Once Daily

H. Pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy:

Nexpro	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

DIRECTION FOR USE

SWALLOW WHOLE OR DIVIDED HALF OF THE TABLET, DO NOT CHEW OR CRUSH.

OVERDOSAGE

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

Store below 30^{o}C.

PRESENTATION

Nexpro-20: It is available as brown coloured, round, biconvex film-coated tablets with break line on one side, in strip of 10 tablets.

Nexpro-40: It is available as brown coloured, round, biconvex film-coated tablets with break line on one side, in strip of 10 tablets.

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Manufactured by :
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