NEXIUM®
Esomeprazole

Tablets 20mg and 40mg

Composition
Each tablet contains: esomeprazole magnesium trihydrate 22.3mg and 44.5mg (corresponding to esomeprazole 20mg and 40mg)

For excipients see “list of excipients”.

Pharmaceutical Form
Gastro-resistant tablets
20mg: a light pink, oblong, biconvex, film-coated tablet engraved 20mg on side and EH on the other side.
40mg: a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and EI on the other side.

Each tablet contains esomeprazole as enteric-coated pellets (MUPS).

Indications
Nexium tablets are indicated for:
Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and
- healing of Helicobacter pylori associated duodenal ulcer.

Dosage and method of administration
The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis: 20-40 mg 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.

Nexium 40mg should only be administered for patients with mucosal break of grade C and
D under the LA classification system. The grade of which, should be confirmed by endoscopical or radiological diagnosis.
Patients who have GERD with erosive esophagitis of grade A and B are recommended to be treated with Nexium 20mg.

- long-term management of patients with healed esophagitis to prevent relapse: 20mg once daily.
- Symptomatic treatment of gastroesophageal reflux disease (GERD): 20mg once daily in patients without esophagitis. If symptoms control has not been achieved after four weeks, the patients 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.

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori:
- healing of Helicobacter pylori associated duodenal ulcer: 20mg Nexium with 1g amoxicillin and 500mg clarithromycin, all twice daily for 7 days.

Children
There is no experience with Nexium 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 (see “Pharmacokinetics”)

Impaired hepatic function
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a dose of 20 mg Nexium should be used. (see “Pharmacokinetics”).

Elderly
Dose adjustment is not required in the elderly.

Contraindications
Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Special warnings and special precautions for use
In the presence of any alarm symptoms (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 Nexium 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.

**Interactions**

**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 other acid secretion or antacids, the absorption of ketoconazole and intraconazole can decrease during treatment with esomeprazole.

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. 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 through 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.

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. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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

**Effects of other drugs on the pharmacokinetcs of esomeprazole**

Esomeprazole is metabolized by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarytromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment is not required.

**Use during pregnancy and lactation**

For esomeprazole no clinical data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development.

However, in rabbits, esomeprazole was associated with reduced fetal weight and increased incidence of minor skeletal anomalies, although this effects were most probably related to the
Maternal toxicity of esomeprazole in this species.

Nexium should only be given to pregnant women if its use is considered essential.

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

**Effects on ability to drive and use machines**

No effects have been observed

**Undesirable effects**

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole. None was found to be dose-related.

- **Common** (>1/100, <1/10) Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation.
- **Uncommon** (>1/1000, <1/100) Dermatitis, pruritus, urticaria, dizziness, dry mouth

Rare adverse drug reactions observed with the racemate may be anticipated with esomeprazole. For further information see product information for omeprazole. However, there have been no reports of such reactions in the clinical trials with esomeprazole.

**Overdosage**

There is no experience to date with deliberate overdose. Data are limited but single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively 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.

**Pharmacodynamic properties**

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell.

**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.

**Effects 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. 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.

Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

**Therapeutic effects of acid inhibition**

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d and appropriate antibiotics, result 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.

**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 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.

**Pharmacokinetic properties**

**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 68% after repeated once daily administration. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

**Metabolism and excretion**

Esomeprazole is completely metabolized 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 9L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time – and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by 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 1-2% on 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%.

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

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired, however no dose adjustment is required. 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. 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.

**List of excipitents**
Glyceryl monostearate 40-50 type II, hydroxypropyl cellulose, hypromellose, iron oxide (reddish-brown, yellow) (E 172), magnesium stearate, methacrylic acid ethylacrylate copolymer (1:1), cellulose microcrystalline, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, sugar spheres, talc, titanium dioxide (E 171), triethyl citrate.

**Incompatibilities**
Not applicable.

**Shelf life**
Please see outer carton pack.

**Special precautions for storage**
Store in the original package. Store up to 30°C.

**Package**
Nexium 20 mg : - boxes of 2 blisters @ 7 tablets
  - boxis of 4 blisters @ 7 tablets

Nexium 40 mg : - boxes of 2 blisters @ 7 tablets
  - boxis of 4 blisters @ 7 tablets

**HARUS DENGAN RESEP DOKTER**
Manufactured by : AstraZeneca AB. Sweden,

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