

SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NEXIUM 20 mg gastro-resistant tablets

NEXIUM 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 20 mg or 40 mg esomeprazole (as magnesium trihydrate).

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

20 mg: A light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side.

40 mg: A pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 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 i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

4.2 Posology and method 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 coating 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. For preparation and administration instructions see section 6.6.

Adults and adolescents from the age of 12 years

Gastroesophageal Reflux Disease (GERD)

- treatment of erosive reflux esophagitis

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.

- long-term management of patients with healed esophagitis to prevent relapse

20 mg once daily.

- symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg 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 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 appropriate antibacterial therapeutic regimens 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.

20 mg Nexium 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 i.v. induced prevention of rebleeding of peptic ulcers.

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

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is Nexium 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 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

Nexium 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. (See Section 5.2).

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 Nexium should not be exceeded. (See section 5.2).

Elderly

Dose adjustment is not required in the elderly.

4.3 Contraindications

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

Esomeprazole like other PPIs should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and special precautions for use

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 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.

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. See section 4.5.

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 (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

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.

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. PPIs including esomeprazole should not be co-administered with atazanavir (see section 4.3).

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) C_{max} and AUC_{τ} by 15% and 41%, respectively.

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.

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 (see also section 4.4).

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

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 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. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_τ 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.

4.6 Pregnancy and lactation

For Nexium, clinical data on exposed pregnancies are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. 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 Nexium should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No effects have been observed.

4.8 Undesirable effects

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 (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

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitor

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.

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. 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.

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, 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 randomized, 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 randomized to receive Nexium solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, 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 Nexium for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the Nexium treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the Nexium treated versus the placebo treated group 7.7% vs 13.6%.

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*.

In two studies with ranitidine as an active comparator, Nexium showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, Nexium 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.

5.2 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 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 $2.9 \pm 1.5\%$ 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.

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 (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monostearate 40-55,
hypromellose,
hypromellose,
iron oxide (20mg & 40mg tablets: reddish-brown; 20mg tablets: yellow) (E 172),
magnesium stearate,
methacrylic acid ethylacrylate copolymer (I:I) dispersion 30 per cent,
cellulose microcrystalline,
synthetic paraffin,
macrogols,
polysorbate 80,
crospovidone,
sodium stearyl fumarate,
sugar spheres (sucrose and maize starch),
talc,
titanium dioxide (E 171),
triethyl citrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years
2 years in climate zones III-IV

6.4 Special precautions for storage

Do not store above 30°C.

Keep the container tightly closed (bottle). Store in the original package (blister).

6.5 Nature and content of container

- Polyethylene bottle with a tamper proof, polypropylene screw cap equipped with a desiccant capsule.
- Aluminium blister package.

20 mg, 40 mg: Bottles of 2, 5, 7, 14, 15, 28, 30, 56, 60, 100, 140(5x28) tablets.

20 mg, 40 mg: Blister packs in wallet and/or carton of 3, 7, 7x1, 14, 15, 25x1, 28, 30, 50x1, 56, 60, 90, 98, 100x1, 140 tablets

6.6 Instructions for use and handling, and disposal (if appropriate)

Administration through gastric tube

1. Put the tablet into an appropriate syringe and fill the syringe with approximately 25 mL water and approximately 5 mL air.
For some tubes, dispersion in 50 mL water is needed to prevent the pellets from clogging the tube.
2. Immediately shake the syringe for approximately 2 minutes to disperse the tablet.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe and position it with the tip pointing down. Immediately inject 5 – 10 mL into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip)
6. Turn the syringe with the tip down and immediately inject another 5 – 10 mL into the tube. Repeat this procedure until the syringe is empty.
7. Fill the syringe with 25 mL of water and 5 mL of air and repeat step 5 if necessary to wash down any sediment left in the syringe. For some tubes, 50 mL water is needed.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
151 85 Södertälje

8 NUMBER(S) IN THE COUNTRY REGISTER OF MEDICINAL PRODUCTS

Nexium 20 mg: 15945

Nexium 40 mg: 15946

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 October 2000 / 10 March 2005

10 DATE OF REVISION OF THE TEXT

29 April 2009