

## **DATASHEET**

### **NAME OF MEDICINE**

NEXIUM<sup>®</sup>

20 mg and 40 mg gastro-resistant tablets.

Esomeprazole 20 mg or 40 mg (as magnesium trihydrate)

### **PRESENTATION**

Gastro-resistant tablets 20 mg: A light pink, oblong, biconvex, film-coated tablet engraved 20 mg+ on one side and  $\frac{A}{EH}$  + on the other side. Each tablet contains esomeprazole enteric-coated pellets.

Gastro-resistant tablets 40 mg: A pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and  $\frac{A}{EI}$  on the other side. Each tablet contains esomeprazole enteric-coated pellets.

### **USES**

#### **ACTIONS**

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action as an 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<sup>+</sup>K<sup>+</sup>-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 GORD 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.

Following repeated dose administration of 0.5 mg/kg and 1.0 mg/kg esomeprazole in < 1 month old and 1 to 11 month old infants, respectively, the effect on intragastric pH, expressed as change in percentage of time with intragastric pH>4 from baseline, is similar to that observed after esomeprazole 20 mg in adults. In addition, 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, results in a significant reduction in oesophageal acid exposure.

### **Therapeutic effects of acid inhibition**

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

One week of treatment with esomeprazole 20 mg bid and appropriate antibiotics, results in successful eradication of *Helicobacter pylori* in approximately 90% of patients.

After eradication treatment there is no need for subsequent monotherapy with antisecretory medicines for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

### **Other effects related to acid inhibition**

During treatment with anti-secretory medicines, 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 anti-secretory medicines, 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* and possibly also *Clostridium difficile* in hospitalised patients.

## **PHARMACOKINETICS**

### **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 dosing. 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 polymorphically 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 major 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 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 3% 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 NEXIUM.

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 NEXIUM.

The metabolism of esomeprazole in patients with mild to moderate liver impairment may be impaired. The metabolic rate is decreased in patients with severe liver impairment 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 hepatic impairment. 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 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.

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.

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration ( $t_{max}$ ) for the 10 mg dose was similar across the 1 to 11 year olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year olds compared to 12-18 year olds and adults.

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year olds.

Following repeated dose administration of 1.0 mg/kg esomeprazole in 1 to 11 month old infants, the exposure (AUC) was slightly higher than that observed after 0.5 mg/kg esomeprazole in <1 month old infants, but similar to that observed after 10 mg in 1 to 11 year olds, and 20 mg in 12 to 18 year olds as well as adults.

## INDICATIONS

NEXIUM is highly effective in the treatment of acid related diseases and for the eradication of *Helicobacter pylori* when given in combination with appropriate antibiotics.

NEXIUM is indicated for:

### **Gastro-oesophageal reflux disease (GORD):**

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

### **In combination with 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

## **DOSAGE AND ADMINISTRATION**

NEXIUM 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. 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.

### **Gastro-oesophageal Reflux Disease (GORD)**

- Treatment of Erosive Reflux Oesophagitis

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.

- Long-term management of patients with healed oesophagitis to prevent relapse

20 mg once daily

- Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients without oesophagitis, 20 mg once daily.

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 20 mg once daily when needed. In NSAID treated risk patients subsequent symptom control using on demand treatment is not recommended.

### **In combination with 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

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

### **CHILDREN**

NEXIUM is not recommended for use 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 maximum dose of 20 mg NEXIUM should not be exceeded (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.

**WARNINGS AND PRECAUTIONS**

In the presence of any major 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.

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

When prescribing NEXIUM 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 medicines metabolised via CYP3A4 such as cisapride.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Concomitant administration with esomeprazole and medicines such as atazanavir and nelfinavir is not recommended (see INTERACTIONS).

**PREGNANCY AND LACTATION**

For NEXIUM, limited clinical data on exposed pregnancies is available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with

respect to embryonal/foetal 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.

### **EFFECT ON ABILITY TO DRIVE AND USE MACHINES**

NEXIUM is not likely to affect the ability to drive or use machines.

### **ADVERSE EFFECTS**

The following definitions of frequencies are used:

Common	~ 1/100
Uncommon	~ 1/1,000 and <1/100
Rare	~ 1/10,000 and <1/1,000
Very rare	<1/10,000

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

<b>Blood and lymphatic system disorders</b>	<i>Rare</i>	Leukopenia, thrombocytopenia
	<i>Very rare</i>	Agranulocytosis, pancytopenia
<b>Immune system disorders</b>	<i>Rare</i>	Hypersensitivity reactions eg, angioedema and anaphylactic reaction/shock
<b>Metabolism and nutrition disorders</b>	<i>Uncommon</i>	Peripheral oedema
	<i>Rare</i>	Hyponatraemia
	<i>Very rare</i>	Hypomagnesaemia
<b>Psychiatric disorders</b>	<i>Uncommon</i>	Insomnia
	<i>Rare</i>	Agitation, confusion, depression
	<i>Very rare</i>	Aggression, hallucination
<b>Nervous system disorders</b>	<i>Common</i>	Headache
	<i>Uncommon</i>	Dizziness, paraesthesia, somnolence
	<i>Rare</i>	Taste disturbance

<b>Eye disorders</b>	<i>Rare</i>	Blurred vision
<b>Ear and labyrinth disorders</b>	<i>Uncommon</i>	Vertigo
<b>Respiratory, thoracic and mediastinal disorders</b>	<i>Rare</i>	Bronchospasm
<b>Gastrointestinal disorders</b>	<i>Common</i>	Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
	<i>Uncommon</i>	Dry mouth
	<i>Rare</i>	Stomatitis, gastrointestinal candidiasis
<b>Hepatobiliary disorders</b>	<i>Uncommon</i>	Increased liver enzymes
	<i>Rare</i>	Hepatitis with or without jaundice
	<i>Very rare</i>	Hepatic failure, hepatic encephalopathy
<b>Skin and subcutaneous tissue disorders</b>	<i>Uncommon</i>	Dermatitis, pruritus, urticaria, rash
	<i>Rare</i>	Alopecia, photosensitivity
	<i>Very rare</i>	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
<b>Musculoskeletal, connective tissue and bone disorders</b>	<i>Rare</i>	Arthralgia, myalgia
	<i>Very rare</i>	Muscular weakness
<b>Renal and urinary disorders</b>	<i>Very rare</i>	Interstitial nephritis
<b>Reproductive system and breast disorders</b>	<i>Very rare</i>	Gynaecomastia
<b>General disorders and administration site conditions</b>	<i>Rare</i>	Malaise, hyperhidrosis

## **INTERACTIONS**

### **EFFECTS OF ESOMEPRAZOLE ON OTHER MEDICINES**

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

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Concomitant administration of 30 mg 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 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required in this study. 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, from post marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased  $C_{max}$  and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

In healthy volunteers, concomitant administration of 40 mg NEXIUM 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 WARNINGS AND PRECAUTIONS).

Omeprazole has been reported to interact with some antiretroviral medicines. 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 antiretroviral medicine. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral medicines, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended.

NEXIUM has been shown to have no clinically relevant effects on the pharmacokinetics of 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 MEDICINES ON THE PHARMACOKINETICS OF ESOMEPRAZOLE**

NEXIUM is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure.

However, dose adjustment of esomeprazole is not required in either of these situations.

### **OVERDOSAGE**

The symptoms described in connection with deliberate Nexium overdose (limited experience of doses in excess of 240 mg/day) are transient. 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.

### **TREATMENT OF OVERDOSAGE**

As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

### **PHARMACEUTICAL PRECAUTIONS**

#### **STORAGE CONDITIONS**

Store below 30°C. Keep the container tightly closed (bottle). Store in the original package (blister)

#### **SHELF-LIFE**

3 years

#### **CONTAINER**

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

### **MEDICINE CLASSIFICATION**

Prescription Medicine

### **PACKAGE QUANTITIES**

20 mg: bottles or blister packs of 7, 14, 30 and 100 tablets.  
40 mg: bottles or blister packs of 7, 30 and 100 tablets.

### **FURTHER INFORMATION**

#### **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.

There was no unexpected toxicity and/or other effects following esomeprazole treatment of rats or dogs from the neonatal period, during sucking and beyond weaning, compared to those previously observed in adult animals. Neither were there any findings indicating that neonatal/juvenile animals are more susceptible to proliferative changes in the gastric mucosa following esomeprazole treatment. Thus, there were no findings in these juvenile toxicity studies that indicate any specific risk in the paediatric population.

#### **LIST OF EXCIPIENTS**

Glycerol monostearate 40-55, hydroxypropyl cellulose, hypromellose, iron oxide (reddish-brown, yellow) (E 172), magnesium stearate, methacrylic acid ethylacrylate copolymer (1:1) dispersion 30 per cent, cellulose microcrystalline , synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, sugar spheres (sucrose and maize starch) , talc, titanium dioxide (E 171), triethyl citrate.

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