**NEXIUM MUPS®**
**(esomeprazole)**

# 1. NAME OF THE MEDICINAL PRODUCT

Nexium MUPS®
Esomeprazole
Tablets 20 mg and 40 mg

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Multiple-Unit Pellet System (MUPS) tablet contains: 20 mg or 40 mg esomeprazole (as magnesium trihydrate).

For excipients see "List of excipients".

# 3. PHARMACEUTICAL FORM

**Gastro-resistant tablets**

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 MUPS 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 an 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.

**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. Patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric and/or duodenal ulcers. Controlled studies do not extend beyond 6 months.

**Patients requiring continued low dose aspirin (75-325 mg) therapy**

- Prevention of gastric and/or duodenal ulcers associated with low dose aspirin therapy, in patients at risk.

**Prevention of rebleeding of gastric or duodenal ulcers following treatment with Nexium IV solution by intravenous infusion**

**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 "Instructions for use and handling".

**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.

Controlled studies in adolescence do not extend beyond 8 weeks. Therefore, physicians who elect to use Nexium MUPS in adolescents for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

- Symptomatic treatment of gastroesophageal reflux disease (GERD):

20 mg once daily in patients without esophagitis. If symptom control has not been achieved after four 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 patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

**Adults**

***In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and***

- Healing of *Helicobacter pylori* associated duodenal ulcer:

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

- Prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers:

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

When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment and appropriate use of antibacterial agents.

The treatment should be supervised by a specialist.

The posology recommendation for esomeprazole is the following:
20 mg twice daily for one week.

***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.

***Patients requiring continued low dose aspirin therapy***

- Prevention of gastric and/or duodenal ulcers associated with low dose aspirin therapy in patients at risk:

20 mg or 40 mg once daily.

The therapeutic benefit of esomeprazole 40 mg over esomeprazole 20 mg over the prevention of gastric and/or duodenal ulcers was not demonstrated. Dose of 40 mg can be initiated in patients presented with erosive reflux esophagitis. Refer to posology for erosive reflux esophagitis.

***Prevention of rebleeding of gastric or duodenal ulcers following treatment with Nexium IV solution by intravenous infusion***

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 MUPS 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. Safety information is limited in doses above 80 mg a day. Clinical trial in adults does not extend beyond 12 months for Nexium MUPS doses 80 mg daily or higher. Therefore, physicians who elect to use Nexium MUPS in extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

**Children below the age of 12 years**

Nexium MUPS 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 "Pharmacokinetic Properties").

**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 MUPS should not be exceeded (See "Pharmacokinetic Properties").

**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.

## 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 "Interactions").

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.

Concomitant administration with esomeprazole and drugs such as atazanavir and nelfinavir is not recommended (See "Interactions").

Co-administration of esomeprazole with atazanavir is not recommended (See "Interactions"). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be discouraged (See also the "Interactions").

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

**Bone fracture**

Some published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with a small increased risk for osteoporosis related fractures. The risk of fracture was increased in patients who received high-dose, defined as multiple daily oral doses, and long-term oral PPI therapy (a year or longer). However, in other similar observational studies no such increased risk was found.

In AstraZeneca's randomized, double-blind and controlled clinical studies on omeprazole and esomeprazole (including two open long-term studies of up to more than 12 years) there are no indications that PPIs are associated with osteoporotic fractures.

Although a causal relationship between omeprazole/esomeprazole and osteoporotic fractures has not been established, patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

### *Clostridium difficile* associated diarrhoea

Published observational studies suggest that proton pump inhibitor (PPI) therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile* associated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (See "Undesirable effects").

CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxillin) indicated for use in combination with esomeprazole, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

### Concomitant use of esomeprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may need to be considered in some patients (See "Interactions").

### Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (See "Undesirable Effects").

### Cutaneous lupus erythematosus and Systemic lupus erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients

ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Nexium, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

## 4.5 Interaction with other medical products and other forms of interaction

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

The gastric acid suppression during treatment with esomeprazole and other PPIs, might decrease or increase the absorption of drugs with a gastric pH dependent absorption. Like with other drugs that decrease the intragastric acidity, the absorption of drugs, such as ketoconazole, itraconazole and erlotinib can decrease while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

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. Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that 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 coumarine derivatives.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a

decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. 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 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 "Special warnings and special precautions for use").

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (See “Special warnings and special precautions for use”).

Omeprazole has been reported to interact with some antiretroviral drugs. 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 drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, 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 drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs 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 drugs such as atazanavir and nelfinavir is not recommended.

Esomeprazole 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 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 CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. A dose adjustment of esomeprazole is not required in either of these situations. However, a dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

## 4.6 Pregnancy and lactation

For Nexium, limited data on exposed pregnancies are available. With the racemic mixture omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative or foetotoxic events. 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 Nexium 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 or 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 administered orally or intravenously and post-marketing when administered orally. 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); not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders**

Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia

**Immune system disorders**

Rare: Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock
Not known: Systemic lupus erythematosus

**Metabolism and nutrition disorders**

Uncommon: Peripheral oedema
Rare: Hyponatraemia
Very Rare: Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia
Hypomagnesaemia may also result in hypokalaemia

**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**

Uncommon: 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
Very rare: Microscopic colitis

**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), acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: Cutaneous lupus erythematosus

**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

**Infection and Infestation**

Not Known: In hospitalized patients, *Clostridium difficile* associated diarrhea

## 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 Helicobacter 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 haemostasis, 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 was 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. Also chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement**.** Measurements should be repeated if levels have not normalised by this time.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in patients during long-term treatment with orally administered esomeprazole. In over 1,000 patients treated with NEXIUM up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

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* and, in hospitalised patients, possibly also *Clostridium difficile*.

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.

**Patients requiring continued low dose aspirin therapy**

Prevention of gastric and/or duodenal ulcers associated with low dose aspirin therapy in patients at risk.

NEXIUM was significantly better than placebo in prevention of gastric and/or duodenal ulcers associated with low dose aspirin therapy in patients at risk (prior history of ulcer disease, age >60 years with a history of coronary artery disease or age >65 years).

## 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 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 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.

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***

The efficacy in paediatric population is extrapolated from the efficacy in adult population based on the pharmacokinetic profile of esomeprazole in adolescent population relative to adult population.

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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Glycerol monostearate 40-55, hyprolose, hypromellose, iron oxide (20 mg & 40 mg tablets: reddish-brown, 20 mg tablets: yellow) (E 172), magnesium stearate, methacrylic acid ethyl acrylate copolymer (1:1), microcrystalline cellulose, macrogols, polysorbate 80, crospovidone, sodium stearyl fumarate, sugar spheres (sucrose and maize starch), talc, titanium dioxide (E 171), triethyl citrate, synthetic paraffin.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Please refer to expiry date on the blister or outer carton.

## 6.4 Special precautions for storage

Store in the original package. Do not store above 30°C.

## 6.5 Pack Size

Please refer to the outer carton for pack size.

## 6.6 Instructions for use and handling

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.

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