AUSTRALIAN PRODUCT INFORMATION

NEXIUM®

(esomeprazole magnesium trihydrate)

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). 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 via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a

few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

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

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

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. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

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

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. 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 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

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

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage 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.

4.3 CONTRAINDICATIONS

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

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, 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 esomeprazole 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Effects of acid inhibition

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*.

Concomitant therapy with clopidogrel

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 avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue esomeprazole if acute tubulointerstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. 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 during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their prescriber immediately when observing any indicative signs or symptoms. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

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.

Use in the Elderly

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

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	**40 mg**	**20 mg**	**40 mg**
AUC (µmol.h/L)	3.65	13.86	4.2	12.6
C_{max} (µmol/L)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{½}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{½}$, and median value for t_{max}

Children 1-11 years

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 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	**10 mg (n=8)**	**10 mg (n=7)**	**20 mg (n=6)**
AUC (μmol.h/L)	0.74	4.83	3.70	6.28
C_{max} (μmol/L)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{½}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

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

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 μmol.h/L for the 1.0 mg/kg dose and 0.65 μmol.h/L for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 μmol/L and 0.17 μmol/L were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_{τ}, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH>4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

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.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely 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 plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

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 dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), 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.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) 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 avoided.

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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

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, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

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.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

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 (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

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. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

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-

marketing 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.

Tacrolimus

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

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

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 nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) 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 avoided.

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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, 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 drugs such as ketoconazole, itraconazole and erlotinib can decrease and 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 can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 μmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear 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

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

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

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

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)

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis
Not known: withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	**136**	**147**	**144**	**115**	**58**
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. 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 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

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 GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least: 8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* $p < 0.001$

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6 Mean time intragastric pH >4 and % patients with intragastric pH >4 for at least 12 hours for different treatment regimens in symptomatic GORD patients over 24 hours

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80

mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

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 (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to 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. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system[Ψ]) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

[Ψ] **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	0.0002
Week 8	Grade A	93.7%	92.5%	
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	0.018

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit

(Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days

compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.

	NEN-0001	NEN-0003
Statistic	**E20 vs placebo**	**E20 vs placebo**
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non- selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

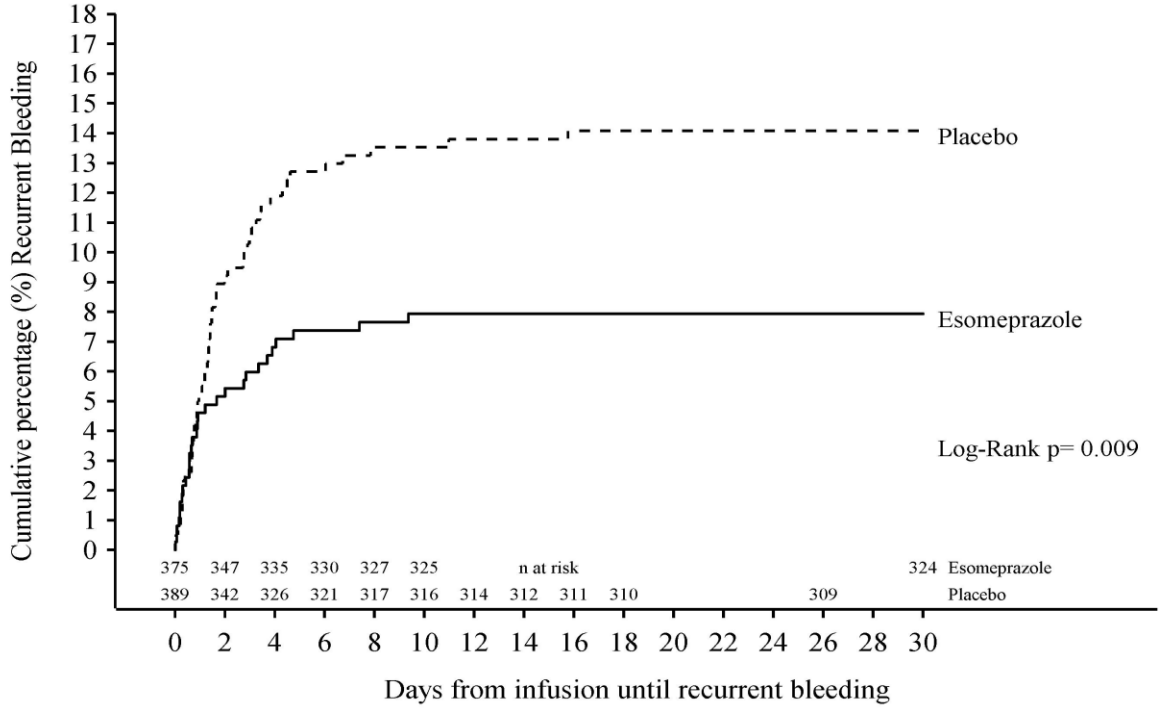
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs

13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with

placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the 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.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

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

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. 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.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of 1gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid

copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, crospovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7#, 15#, 30, and 100# tablets.

#non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

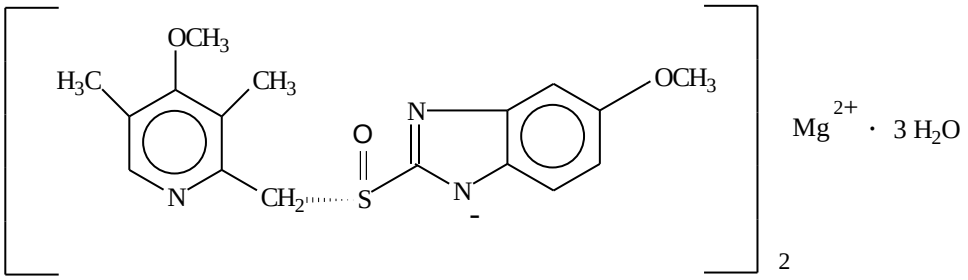
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg.3H_2O$

Molecular weight

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

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Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

18 June 2025

Summary table of changes

Section changed	Summary of new information
4.4	Updated to include a warning under severe cutaneous adverse reactions (SCARs).
6.5	Updated the market availability of pack size 7.

NEXIUM® is a registered trade mark of the AstraZeneca group of companies.

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