AUSTRALIAN PRODUCT INFORMATION
NEXIUM® IV (esomeprazole sodium)
powder for solution

1. NAME OF THE MEDICINE

Esomeprazole sodium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM IV is esomeprazole sodium, a substituted benzimidazole. NEXIUM IV consists of a 5 mL vial containing lyophilised esomeprazole sodium 42.5 mg (equivalent to 40 mg esomeprazole) with disodium edetate and sodium hydroxide for pH adjustment, which is intended to be reconstituted with 5 mL normal saline (injection) or up to 100 mL normal saline (infusion). The reconstituting solution, normal saline, is not supplied with the dosage form. No other reconstituting solution should be used. This presentation may be added to plastic giving sets.

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

3. PHARMACEUTICAL FORM

NEXIUM IV (esomeprazole sodium) is available as a powder for solution that may be administered by either intravenous injection or intravenous infusion.

NEXIUM is also available in 20 mg and 40 mg tablets containing enteric-coated pellets (see separate NEXIUM Product Information).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The short-term management of Gastro-Oesophageal Reflux Disease (GORD) in patients with oesophagitis and/or severe symptoms of reflux as an alternative when oral therapy is inappropriate.

Prevention of rebleeding in patients following therapeutic endoscopy for acute, bleeding gastric or duodenal ulcers.

Short-term management in patients requiring continued non-steroidal anti-inflammatory drug (NSAID) therapy when oral therapy is inappropriate:

- healing of gastric ulcers associated with NSAID therapy
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk

NEXIUM IV should be replaced with oral therapy as soon as practicable.

4.2 DOSE AND METHOD OF ADMINISTRATION

NEXIUM IV should only be used where oral medication is inappropriate (e.g. in severely ill patients).

Treatment with NEXIUM IV can be given for up to 10 days as part of a full treatment period for the specified indications. When oral therapy is possible or appropriate, intravenous therapy with NEXIUM IV should be discontinued and the therapy should be continued orally.

Contains no antimicrobial agent. NEXIUM IV is for single use in one patient only. Discard any remaining contents.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily

The duration of treatment should be 4 weeks. An additional 4 weeks treatment is recommended for patients in whom the oesophagitis has not healed or who have persistent symptoms.

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

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease

20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated.

Short-term management in patients requiring continued non-steroidal anti-inflammatory drug (NSAID) therapy when oral therapy is not appropriate

Healing of gastric ulcers associated with NSAID therapy

20 mg once daily

Prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) therapy in patients at risk

20 mg once daily

Prevention of rebleeding of gastric or duodenal ulcers

Following therapeutic endoscopy, 80 mg administered as bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/hr for a period of 3 days (see Method of administration).

The parenteral treatment period should be followed by oral acid-suppression therapy for a duration to be determined by the treating doctor.

Children and adolescents aged 1-17 years

Treatment with NEXIUM IV can be given as part of a full treatment period for Gastro-Oesophageal Reflux Disease (GORD). When oral therapy is possible or appropriate, intravenous therapy with NEXIUM IV should be discontinued, and the therapy should be continued orally (see NEXIUM Product information for oral administration). Usually intravenous treatment duration should be short and transfer to oral treatment should be made as soon as possible.

The dose should be infused over 10 minutes to 30 minutes.

1 year to 17 years - body weight less than 55 kg

10 mg once daily

1 year to 17 years - body weight 55 kg or greater

20 mg once daily

Method of administration

Injection

A ready to use solution for injection (8 mg/mL) is prepared by adding 5 mL of 0.9% sodium chloride for intravenous use into one 40 mg vial of NEXIUM IV powder. No other reconstituting solution should be used. This solution may be administered directly by intravenous injection. Single use only.

40 mg dose

5 mL of the reconstituted solution (8 mg/mL) should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose

2.5 mL of the reconstituted solution (8 mg/mL) should be given as an intravenous injection over a period of at least 3 minutes.

Infusion (10 mg, 20 mg or 40 mg dose)

40 mg dose

Reconstitute the contents of one 40 mg vial of NEXIUM IV powder with 5 mL of sodium chloride 0.9% for intravenous use. Further dilute this solution in up to 100 mL with sodium chloride 0.9% for intravenous use. No other reconstituting solution should be used. The diluted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Single use only.

20 mg dose

Reconstitute the contents of one 40 mg vial of NEXIUM IV powder with 5 mL of sodium chloride 0.9% for intravenous use. Further dilute **2.5 mL** of this solution in up to 50 mL with sodium chloride 0.9% for intravenous use. No other reconstituting solution should be used. The diluted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Single use only.

10 mg dose

Reconstitute the contents of one 40 mg vial of NEXIUM IV powder with 5 mL of sodium chloride 0.9% for intravenous use. Further dilute **1.25 mL** of this solution in up to 25 mL with sodium chloride 0.9% for intravenous use. No other reconstituting solution should be used. The diluted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Single use only.

Infusion (80 mg dose)

Reconstitute the contents of two 40 mg vials in up to 100 mL 0.9% sodium chloride for intravenous use (esomeprazole concentration of 0.8 mg/mL). No other reconstituting solution should be used.

80 mg bolus dose

The reconstituted solution should be given as an intravenous infusion over a period of 30 minutes. Single use only.

8 mg/h dose

The reconstituted solution should be given as an intravenous infusion at a rate of 8 mg/h and continued for a period of 71.5 hours. Single use only.

Reconstituted solution for injection and infusion

To reduce microbiological hazard, use immediately after reconstitution. Do not store reconstituted preparations.

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). A maximum daily dose of 20 mg NEXIUM IV should not be exceeded in patients with severe liver impairment (Child Pugh C) and GORD or the need for esomeprazole therapy due to concomitant NSAID intake. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours, followed by a maximum dose of 20 mg once daily for the oral treatment regimen may be sufficient (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).

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

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.

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 interstitial nephritis

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

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 and GORD or the need for esomeprazole therapy due to

concomitant NSAID intake. There are no data in relation to the use of esomeprazole (80 mg bolus + 8 mg/h infusion) in patients with hepatic dysfunction. However, based on cross-study comparisons with omeprazole for patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours, followed by a maximum dose of 20 mg once daily for the oral treatment regimen may be sufficient. 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

Safety and efficacy of oral esomeprazole has been assessed in a limited number of children and adolescents with GORD aged from 0 to 17 years. Use of NEXIUM IV for the treatment of GORD in children and adolescents is based on safety data, pharmacokinetic data and modelling. NEXIUM IV 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 oral 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%. Similar differences have been seen for intravenous administration of esomeprazole.

These findings have no implications for the dosage advice for esomeprazole.

Gender

Following a single oral 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. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

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), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

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 (t½) 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.

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.

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

Amoxycillin 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 to esomeprazole after an oral dose.

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.

No effects on the fetuses were observed in an embryo-fetal toxicity study in the rat at oral esomeprazole doses of up to 800 µmol/kg (280 mg/kg). The exposure in these animals (plasma AUC) was similar to the daily exposure anticipated in a patient treated with an 80 mg bolus over 30 minutes followed by a continuous intravenous infusion of 8 mg/h over the following 3 days, and was about 6 to 8 times higher than that in adults or adolescents given 40 mg esomeprazole as a 3 minute intravenous injection.

However, in rabbits, esomeprazole at oral doses of up to 250 µmol/kg.day 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 (partial or complete anorexia, leading to body weight loss) in this species. The exposure in these animals was 0.004 times the daily exposure anticipated in a patient treated with an 80 mg bolus over 30 minutes followed by a continuous intravenous infusion of 8 mg/h over the following 3 days, and was about 0.03 to 0.04 times that in adults or adolescents given 40 mg esomeprazole as a 3 minute intravenous injection.

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

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated. Adverse reactions, arising from intravenous use, are provided for esomeprazole (see Clinical trials and post-marketing data) and for the racemate, omeprazole independent of the dose (see Post-marketing data for the racemate (omeprazole)), consistent with the pharmacology and clinical use of these

pharmaceuticals. Most adverse reactions reported with omeprazole have been mild and transient and there has been no consistent relationship with treatment.

Clinical trials and post-marketing data

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and/or from post-marketing use. 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, 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	agitiation, confusion, depression
Very rare	aggression, hallucination

Nervous system disorders

Common	headache
Uncommon	dizziness, parasthesia, somnolence
Rare	taste disturbance

Eye disorders

Rare	blurred vision, visual accommodation disturbances

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

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

Common	administration site reactions
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	interstitial nephritis

Reproductive system and breast disorders

Very rare	gynaecomastia

General disorders and administration site conditions

Rare	malaise, hyperhidrosis

Post-marketing data for the racemate (omeprazole)

Other adverse drug reactions not observed with NEXIUM but which have been observed for the racemate (omeprazole) may also occur with NEXIUM.

The following adverse reactions have been observed for the racemate (omeprazole) and may also occur with esomeprazole:

Other

Very rare	fever, impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children)

Gastrointestinal

Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Endocrine

Very rare	impotence (although causality has not been established)

Loss of vision has been reported in isolated cases in association with the use of intravenous omeprazole. These cases involved critically ill patients who received high doses of omeprazole as an intravenous bolus injection. A causal relationship has not been established.

Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours). In the non-clinical program for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection was noted. The non-clinical findings somewhat indicated that the clinical tissue irritation was concentration related.

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 NEXIUM overdose (limited experience of oral doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 100 mg NEXIUM 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.

Reports of overdosage with omeprazole in humans may also be relevant. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMCODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. Esomeprazole 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 and more sustained 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 effect is similar irrespective of whether esomeprazole is administered orally or intravenously. 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 1 % 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, after oral administration of esomeprazole.

The acid inhibitory effects of IV (30-minute infusion) and oral esomeprazole were compared in three separate trials involving healthy subjects (n=76). The effect on intragastric pH of IV esomeprazole, 20 mg and 40 mg, was similar to that of oral esomeprazole, 20 mg and 40 mg, in all three trials. The percentage of time with intragastric pH >4 during 24 hours after IV and oral administration of esomeprazole is shown in Table 2.

Table 2 Estimated mean (95% CI) percentage of time with intragastric pH >4 during 24 hours after administration of esomeprazole

	Esomeprazole 20 mg			Esomeprazole 40 mg		
Day	**IV 30 min Infusion**	**Oral**	**Difference IV-oral**	**IV 30 min infusion**	**Oral**	**Difference IV-oral**
1	30.4 (24.6-36.2)	27.5 (21.7-33.3)	2.9 (-1.0-6.9)	42.1 (35.2-49.1)	36.5 (29.6-43.5)	5.6 (1.2-10.0)
5	49.5 (41.9-57.2)	51.1 (43.5-58.7)	-1.5 (-7.8-4.7)	66.2 (62.4-70.0)	63.6 (59.7-67.4)	2.6 (-0.5-5.8)

The 20 mg data is derived from trial NEP-0008 (n=24), and the 40 mg data is derived from study NEP-0002 (n=40)

The acid inhibitory effects of a 3-minute injection and a 30-minute infusion of IV esomeprazole 40 mg were compared in 42 healthy subjects. The percentage of time with intragastric pH >4 during 24 hours after the different administration modes of IV esomeprazole 40 mg is described in Table 3. The mean percentage difference of time with intragastric pH >4 between the 3-minute injection and 30-minute infusion (injection minus infusion) was less than 2% both after single and repeated dosing and is considered to be of no clinical relevance. Different IV administration rates for the 20 mg dose of esomeprazole were not compared, however it is assumed that the various administration rates of IV esomeprazole 20 mg will also be similar in acid inhibitory effect.

Table 3 Estimated mean (95% CI) percentage of time with intragastric pH >4 during 24 hours after administration of intravenous esomeprazole 40 mg

	Esomeprazole 40 mg		
Day	**Intravenous 3-min injection**	**Intravenous 30-min infusion**	**Difference injection-infusion**
1	32.3 (26.6-38.0)	33.1 (27.3-38.8)	-0.8 (-4.0-2.4)
10	57.2 (52.8-61.6)	55.6 (51.2-60.0)	1.6 (-1.7-4.9)

During intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/hr for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours and 11-13 hours respectively over 24 hours in healthy subjects.

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 of oral treatment (see NEXIUM Product Information).

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 orally administered esomeprazole.

During long-term oral 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 reversible.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

A randomised, double-blind, multiple placebo, parallel-group trial (n=246) was evaluated to assess the safety and efficacy of three different modes of administration of esomeprazole 40 mg (injection, infusion and oral) in patients with erosive reflux oesophagitis (RO). During the first week of treatment, patients received daily a 3-minute injection, a 30-minute infusion, or orally esomeprazole 40 mg. The first week was then followed by an open treatment period with oral esomeprazole 40 mg daily for 3 weeks. The primary objective was to evaluate safety after 1 week's treatment of IV esomeprazole 40 mg given as injection or infusion. The secondary objectives were to evaluate safety after 4 weeks treatment and efficacy in healing erosive reflux oesophagitis after 4 weeks esomeprazole treatment. Healing of erosive RO was assessed by endoscopy and was defined as absence of mucosal breaks (not present according to the LA classification).

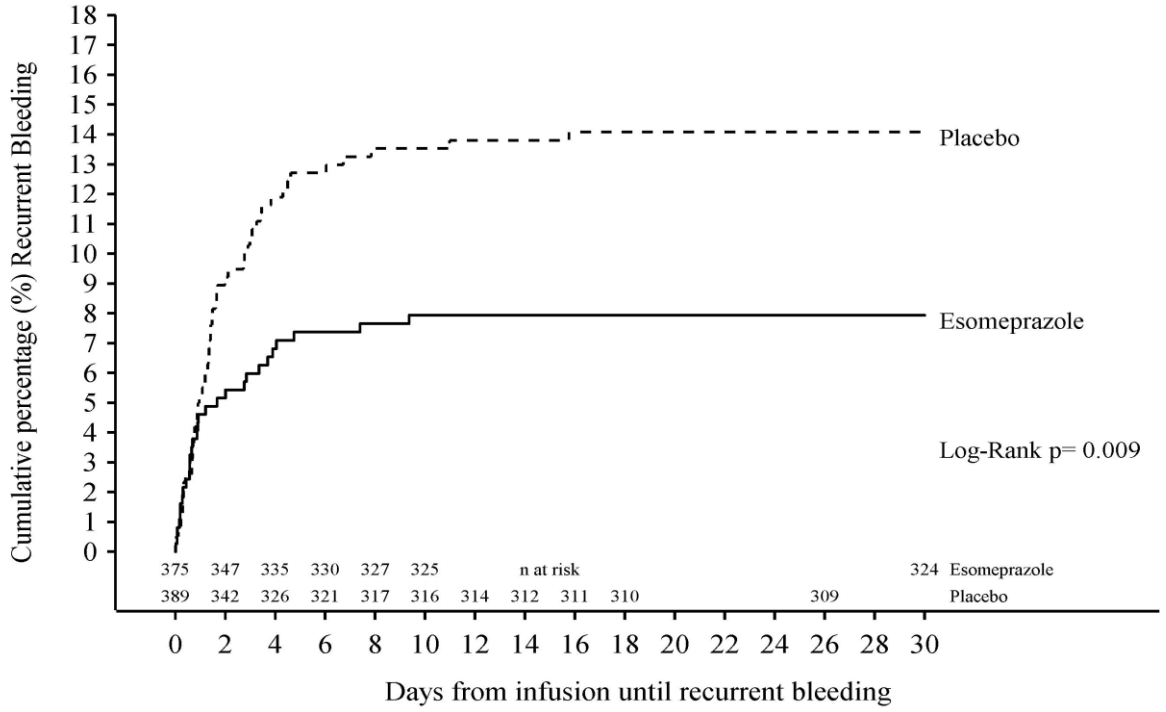
The frequency and type of adverse events at week 1 and week 4 were similar across treatment groups. It was concluded that esomeprazole given intravenously, either as an injection or infusion, has a safety profile similar to that of oral esomeprazole.

At week 4, the proportion of patients in the ITT/safety population with healed erosive RO was 79.7%, 80.2% and 82.6%, respectively, in the injection+oral, infusion+oral and oral treatment groups. Using historical data, the observed healing rates were similar to previous findings with oral esomeprazole, where it was found that the healing rate with once daily esomeprazole 40 mg is approximately 78% at 4 weeks and 93% after 8 weeks of treatment (see NEXIUM Product Information). Given that the trial was not powered for efficacy, the results indicate that 1-week IV (either as injection or infusion) followed by 3 weeks of oral esomeprazole 40 mg treatment has a similar effect on healing of erosive RO as 4 weeks of treatment with oral esomeprazole 40 mg.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomized, 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.

5.2 PHARMACOKINETIC PROPERTIES

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.

Paediatric population

In a randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 50 paediatric patients 0 to 17 years old inclusive. Esomeprazole plasma AUC values for 20 mg NEXIUM IV were 183% and 60% higher in paediatric patients aged 6-11 years and 12-17 years respectively compared to the adults given 20 mg. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 10 mg for patients 1-17 years with body weight <55 kg, and 20 mg for patients 1-17 years with body weight >55 kg would achieve comparable steady-state plasma exposures (AUC_{0-24}) to those observed in adult patients administered 20 mg of NEXIUM IV once every 24 hours. Further, increasing the infusion duration from 3 minutes to 10 minutes or 30 minutes was predicted to produce steady-state C_{max} values that were comparable to those observed in adult patients at the 40 mg and 20 mg NEXIUM IV doses.

5.3 PRECLINICAL SAFETY DATA

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.

Preclinical studies on esomeprazole reveal no particular hazard for humans, based on conventional studies of single and repeated dose toxicity, embryo-foetal toxicity and mutagenicity. As in the oral studies, repeated intravenous administration of esomeprazole to animals resulted in few and primarily mild effects. However, very high intravenous doses caused an acute toxic response that consisted of occasional, nonspecific and short-lived CNS signs. This effect appeared to be associated with the C_{max} rather than the AUC of esomeprazole. Comparison of the C_{max} values in humans given 40 mg as a 3-minute injection or 80 mg as a 30 minute infusion and the plasma concentrations that were acutely toxic in animals showed a wide margin of safety (at least 6-fold for total and 20-fold for unbound plasma concentrations).

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, three oral *in vivo* tests (an oral mouse micronucleus test, an oral chromosome aberration test in rat bone marrow and an intravenous chromosomal aberration test in mouse 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

No carcinogenicity studies have been conducted on esomeprazole. However, long-term treatment with 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 of esomeprazole. 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, nor in a 26-week study in wild type and heterozygous p53+/- knockout mice (at a maximum tolerated dose that was 90-fold the maximum clinical dose, on a mg/m^2 basis), although gastric cell hyperplasia occurred. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric 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

Each vial of NEXIUM IV contains esomeprazole sodium 42.5 mg, equivalent to 40 mg esomeprazole, disodium edetate 1.5 mg and sodium hydroxide q.s. for pH adjustment.

6.2 INCOMPATABILITIES

The degradation of the reconstituted solution is highly pH dependent and the product must therefore only be reconstituted with 0.9% sodium chloride for intravenous use according to the instructions (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Method of administration). The reconstituted solution should not be mixed or coadministered in the same infusion set with any other drug.

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

NEXIUM IV should be stored at room temperature in the outer container, which it is provided in, since this protects the vial from light. Vials can be stored exposed to normal in-door light, for up to 24 hours outside the box.

Store below 25°C and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM IV is available in a pack size of 10 x 5 mL vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

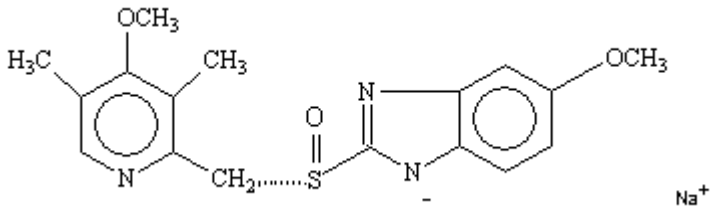
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is (S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 *H*-benzimidazole sodium. 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 sodium is:



CAS number

161796-78-7

Molecular formula

$C_{17}H_{18}N_3O_3SNa$

Molecular weight

367.4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

27 July 2004

10. DATE OF REVISION

16 December 2022

Summary table of changes

Section changed	Summary of new information
4.4	New precaution – hypomagnesaemia.
4.8	Updated adverse effect – hypomagnesaemia.