AUSTRALIAN PRODUCT INFORMATION

NOXICID® CAPS HEARTBURN RELIEF

Esomeprazole (as magnesium) enteric capsule

1 NAME OF THE MEDICINE

Esomeprazole magnesium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NOXICID CAPS HEARTBURN RELIEF is esomeprazole magnesium, a substituted benzimidazole.

The NOXICID CAPS HEARTBURN RELIEF 20 mg enteric capsules are comprised of enteric coated pellets containing esomeprazole (as magnesium).

Each capsule contains esomeprazole magnesium 22.252 mg (equivalent to esomeprazole 20 mg).

List of excipients with known effect: NOXICID CAPS HEARTBURN RELIEF also contains traces of sulfites.

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

3 PHARMACEUTICAL FORM

NOXICID CAPS HEARTBURN RELIEF 20 mg enteric capsule: White to cream coloured pellets filled in hard gelatin capsule with pink cap and pink body, imprinted with 'Mylan' over 'EM 20' in black ink on cap and body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NOXICID CAPS HEARTBURN RELIEF are indicated for:

The symptomatic relief of frequent heartburn and other symptoms of gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Esomeprazole magnesium enteric capsules should be swallowed whole with liquid.

For patients who cannot swallow, the enteric capsules can be opened and pellets mixed 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.

Adults

Relief of heartburn and other symptoms of gastro-oesophageal reflux disease (GORD).

The recommended dose for symptomatic relief of GORD is one NOXICID CAPS HEARTBURN RELIEF 20 mg capsule once daily for 7 – 14 days, depending on the severity and persistence of symptoms.

Patients should be referred to their doctor if symptoms persist or worsen while taking this course, or if symptoms persist or recur within two weeks of completing the course. If symptom control has not been

achieved or relapse has occurred after 14 days treatment with NOXICID CAPS HEARTBURN RELIEF 20 mg capsule daily, further investigation is recommended. Use for longer than 14 days should only be on medical advice.

Not recommended for use in children and adolescents under 18 years of age.

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 esomeprazole magnesium 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 (see 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.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may

lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Patients should be referred to their doctor for review if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena; and when gastric ulcer is suspected or present, as treatment with esomeprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- They are being treated for gastro-oesphageal reflux (heartburn) or gastro-oesophageal reflux disease (GORD) and symptoms persist for more than 14 days.
- Their symptoms persist or recur within two weeks of completing a course of esomeprazole.
- They have any other significant medical conditions.
- They are an adolescent or child under the age of 18 years.

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 esomeprazole. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

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. In case of

clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

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 esomeprazole magnesium.

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)).

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

NOXICID CAPS HEARTBURN RELIEF is not intended for use in children under the age of 18.

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 Cmax 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}.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5-14 days before CgA measurements and that measurements should be repeated if levels have not normalised by this time.

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Effects of esomeprazole on other drugs), 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.

Other drugs that affect 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.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamics (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 + 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.

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.

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of 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 – Pregnancy Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. Esomeprazole magnesium 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 foetal 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 foetuses 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, esomeprazole magnesium 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)

Esomeprazole magnesium 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; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

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

Frequency 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)

Frequency 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

Table 2 Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)

Mean exposure time (days):	**E total N=519 136**	**E 40 N=173 147**	**E 20 N=179 144**	**E 10 N=167 115**	**Placebo N=169 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 any 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 dialysable. 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

NOXICID CAPS HEARTBURN RELIEF (esomeprazole magnesium) 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 3 % 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%

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.

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 4.

Table 4 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

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

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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Once esomeprazole magnesium 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 50% after a single dose of 20 mg and increases to 68% after repeated once daily administration.

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 esomeprazole magnesium 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 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

The inactive ingredients: sugar spheres (ARTG PI No: 2535) , crospovidone, hyprolose, mannitol, methacrylic acid - ethyl acrylate copolymer (1:1), triethyl citrate, glycerol monostearate, sodium hydroxide, sucrose, polysorbate 80 and purified talc. The enteric capsules are comprised of the following: Empty Hard Gelatin Capsule Shells Cap & Body – Pink & Pink Size 3 (ARTG PI No:109606) and TekPrint SW-9008 Black Ink (ARTG PI No: 2328).

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

NOXICID CAPS HEARTBURN RELIEF enteric capsules: stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PA/Al/PVC/Al Foil blisters, these blister packs comprise 7 & 14 capsules.

Australian Register of Therapeutic Goods (ARTG)

AUST R 336014 – NOXICID CAPS HEARTBURN RELIEF esomeprazole 20mg (as magnesium) enteric capsule blister pack

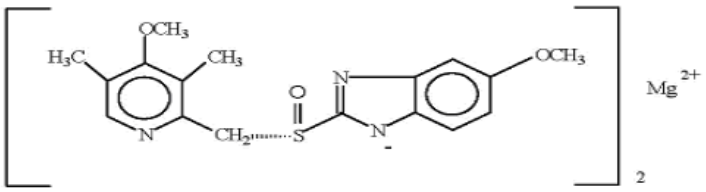
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure



CAS number

CAS Registry Number: 161973-10-0

Molecular formula

$C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight

713.12 (anhydrous)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 (Pharmacy Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

8/5/2020

10 DATE OF REVISION

27/03/2023

Summary table of changes

Section Changed	Summary of New Information

4.4	Addition of hypomagnesaemia
6.1	Correction to ARTG PI No
6.5	Insert AUST R numbers
8	Update sponsor details

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NOXICID CAPS HEARTBURN RELIEF_pi\Mar23/00