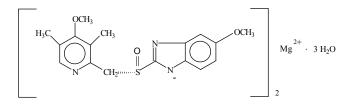


# NAME OF THE MEDICINE

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

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: C<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Mg.3H<sub>2</sub>O

Molecular weight: 767.2 (trihydrate)

# DESCRIPTION

The NEXIUM 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, 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.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

# PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H<sup>+</sup>, K<sup>+</sup>-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 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.

In separate comparative studies (Table 2) 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 2 Time and % patients with intragastric pH>4 for different treatment regimens

				ts with int •4 for at le	
Population	Study drug	Time Intragastric pH>4	8 hours	12 hours	16 hours
Symptomatic	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
GORD (n=31)	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
(n=30)	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy	Esomeprazole 40 mg	14.6 hours	-	77%	32%
(n=22)	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 3.

# Table 3

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

# Table 4Means and mean differences in percentage of time with<br/>intragastric pH>4 on Day 5 following repeated once daily<br/>administration of 20, 40 and 80 mg esomeprazole and<br/>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 TRIALS).

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 and DOSAGE AND 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 antisecretory 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.

# Pharmacokinetics

#### 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.

# **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<sup>♥</sup>) 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 5).

# 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 5).

#### Table 5 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.

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

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

# 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 40 mg 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 40 mg 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 6. 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 CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

# Table 6 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
	Grade A	83.9%	83.1%	
	Grade B	80.2%	75.4%	
Week 4	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	0.0002
	Grade A	93.7%	92.5%	
	Grade B	92.3%	90.4%	
Week 8	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% Cl, 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 7 below.

# Table 7 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%	
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 oesophagitis 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 multi-centre, 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, 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 8). 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 8Difference between esomeprazole and placebo in mean<br/>change in the upper GI symptom score from the last 7<br/>days in the run-in-period to the last 7 days

Statistic	NEN-0001 E20 vs placebo	NEN-0003 E20 vs placebo
Estimated mean difference <sup><math>\Omega</math></sup>	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

 $^{\Omega}$  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, multi-centre, 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  $\geq$ 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, multi-centre, 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 1,429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1,067 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.

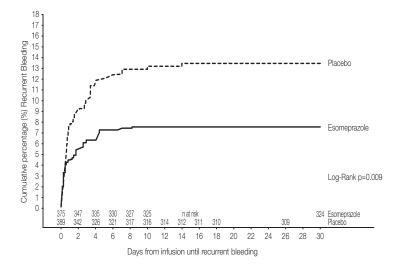
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. 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 amoxycillin 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxycillin 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.

# 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 antiinflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with nonsteroidal 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

# 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 Effects of esomeprazole on other drugs).

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

# PRECAUTIONS

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 Interactions with other medicines).

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.

# 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.

#### Elderly

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

# 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 9).

#### Table 9 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<sup>§</sup>

	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 <sub>max</sub> (µmol/L)	1.45	5.13	2.1	4.7
t <sub>max</sub> (h)	2.00	1.75	1.6	1.6
t <sub>½</sub> (h)	0.82	1.22	1.2	1.5

<sup>§</sup>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,  $C_{\text{max}}$  and  $t_{\mbox{\tiny M2}}$  , and median value for  $t_{\text{max}}$ 

#### 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 10 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 <sub>max</sub> (µmol/L)	0.62	2.98	1.77	3.73
t <sub>max</sub> (h)	1.33	1.44	1.79	1.75
t <sub>½</sub> (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except  $t_{\mbox{\scriptsize max}}$  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 (tmax) 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<sub> $\tau$ </sub> was 3.51 µmol.h/L for the 1.0 mg/kg dose and 0.65  $\mu mol.h/L$  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<sub>t</sub>, AUC<sub>1</sub>, and C<sub>SSmax</sub> 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.

#### 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.

#### Hepatic insufficiency

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 DOSAGE AND ADMINISTRATION).

#### 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.

#### 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<sup>2</sup> 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<sub>2</sub>-receptor antagonists and by partial fundectomy.

# 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*.

# 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  $\mu$ mol/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.

# Effects on ability to drive and operate machinery

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

#### Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P450 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. This should be considered especially when prescribing esomeprazole for on-demand therapy.

#### 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 concentrationtime curve (AUC) and a 31% prolongation of elimination half-life ( $t_{22}$ ) 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 PRECAUTIONS).

#### **Cilostazol**

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a crossover 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 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.

#### <u>Diazepam</u>

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.

#### 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 ketoconazole and itraconazole can decrease and the absorption of \*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).

#### Potential interactions that have been excluded

#### Amoxycillin or quinidine

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

#### \*Effect 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 five days before CgA measurements.

# **ADVERSE 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:  $\geq 10\%$ ; common:  $\geq 1\%$  and < 10%; uncommon:  $\geq 0.1\%$  and < 1%; rare  $\geq 0.01\%$  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

#### 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

Common:	abdominal pain, diarrhoea, flatulence, nausea/vomiting, constibution
Uncommon: Rare:	dry mouth stomatitis, gastrointestinal candidiasis

#### 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)

# Muskuloskeletal, 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 11 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)

#### DOSAGE AND 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 noncarbonated 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 noncarbonated 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 (nonselective 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 the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxycillin 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 oesophagitisWeight <20 kg:</td>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.

# Geriatrics

Dose adjustment is not required in the elderly.

# Hepatic insufficiency

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 PRECAUTIONS).

# **Renal insufficiency**

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.

# OVERDOSAGE

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.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

# PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablet: 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 entericcoated pellets.

NEXIUM 40 mg tablet: 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 entericcoated pellets.

NEXIUM 10 mg granules for oral suspension: 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.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15<sup>#</sup>, 30, and 100<sup>#</sup> tablets and HDPE bottles of 100<sup>#</sup> tablets. Keep bottle tightly closed. <sup>#</sup>non-marketed pack size

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

# NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd ABN 54 009 682 311 Alma Road NORTH RYDE NSW 2113

# POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

# DATE OF APPROVAL

Date of TGA approval: 22 December 2010

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

# \*Please note changes in Product Information

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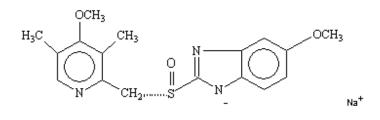
NEXIUM<sup>®</sup> IV (INTRAVENOUS INJECTION AND INTRAVENOUS INFUSION) esomeprazole sodium

# **PRODUCT INFORMATION**

# NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM IV is esomeprazole sodium, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is (S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 *H*-benzimidazole sodium.

The chemical structure of esomeprazole sodium is:



CAS Number: 161796-78-7

Molecular formula: C17H18N3O3SNa

Molecular weight: 367.4

# DESCRIPTION

NEXIUM IV (esomeprazole sodium) is available as a powder for solution that may be administered by either intravenous injection or intravenous infusion. Each vial contains esomeprazole sodium 42.5 mg, equivalent to 40 mg esomeprazole, disodium edetate 1.5 mg and sodium hydroxide q.s. for pH adjustment.

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

# PHARMACOLOGY

Esomeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H<sup>+</sup>, K<sup>+</sup>-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
0000	Omeprazole 20 mg	67%	45%	14%
GORD (n=36)	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD	Omeprazole 40 mg	96%	77%	45%
(n=115)	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		mg	
Day	IV 30 min Infusion	Oral	Difference IV-oral	IV 30 min infusion	Oral	Difference IV-oral
1	30.4	27.5	2.9	42.1	36.5	5.6
	(24.6-36.2)	(21.7-33.3)	(-1.0-6.9)	(35.2-49.1)	(29.6-43.5)	(1.2-10.0)
5	49.5	51.1	-1.5	66.2	63.6	2.6
	(41.9-57.2)	(43.5-58.7)	(-7.8-4.7)	(62.4-70.0)	(59.7-67.4)	(-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.

#### Pharmacokinetics

#### 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.

# **CLINICAL TRIALS**

# Gastro-Oesophageal Reflux Disease (GORD)

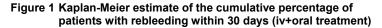
A randomised, double-blind, multiple placebo, parallel-group trial (n=246) was evaluated to assess the safety and efficacy of three different modes of administration of esomeprazole 40 mg (injection, infusion and oral) in patients with erosive reflux oesophagitis (RO). During the first week of treatment, 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).

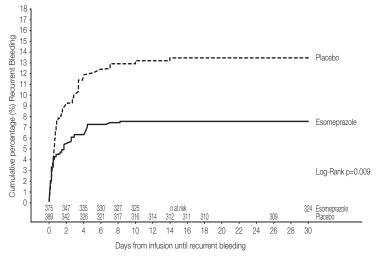
The frequency and type of adverse events at Week 1 and Week 4 were similar across treatment groups. It was concluded that esomeprazole given intravenously, either as an injection or infusion, has a safety profile similar to that of oral esomeprazole.

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.





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.

# 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.

# 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 Interactions with other medicines).

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

# PRECAUTIONS

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.

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.

# 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 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.

#### Elderly

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

# 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.

# Hepatic insufficiency

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 DOSAGE AND ADMINISTRATION).

# **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.

#### Carcinogenesis, mutagenesis, impairment of fertility

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).

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<sup>2</sup> 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 26week 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<sup>2</sup> 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<sub>2</sub>-receptor antagonists and by partial fundectomy.

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*.

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.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 mmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) similar to and 0.004 times the anticipated clinical value]. 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.

#### 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.

#### Effects on ability to drive and operate machinery

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

#### Interactions with other Drugs

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P450 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.

# 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 concentrationtime curve (AUC) and a 31% prolongation of elimination half-life ( $t_{2}$ ) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

#### **Cilostazol**

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a crossover 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 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.

#### <u>Diazepam</u>

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.

# 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 ketoconazole and itraconazole can decrease and the absorption of \*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).

#### Potential interactions that have been excluded

#### Amoxycillin or quinidine

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

#### \*Effect 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 five days before CgA measurements.

# **ADVERSE EFFECTS**

NEXIUM is well tolerated. Adverse reactions, arising from intravenous use, are provided for esomeprazole (see Clinical trials and postmarketing 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 postmarketing use. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common:  $\geq 10\%$ ; common:  $\geq 1\%$  and < 10%; uncommon:  $\geq 0.1\%$  and < 1%; rare  $\geq 0.01\%$  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

#### 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 and mediastinal disorders Rare: bronchospasm

#### Gastrointestinal disorders

Common:	abdominal pain, diarrhoea, flatulence, nausea/vomiting,
	constipation
Uncommon:	dry mouth
Rare:	stomatitis, gastrointestinal candidiasis

#### Hepatobiliary disorder

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)

#### 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

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Very rare: fever, impaired renal function, including nephrosis,
dyspnoea, weight increase and hypokalaemia (reported
in children)
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# 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 nonclinical findings somewhat indicated that the clinical tissue irritation was concentration related.

# DOSAGE AND 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.

# 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 nonsteroidal 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 nonsteroidal 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 acidsuppression therapy for a duration to be determined by the treating doctor.

# Method of administration

# Injection

A ready to use solution for injection is prepared by adding 5 mL of 0.9% sodium chloride for intravenous use into the vial containing the dry powder. No other reconstituting solution should be used. This solution may be administered directly by intravenous injection. Single use only.

# 40 mg dose

The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes.

#### 20 mg dose

Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes.

# Infusion (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 reconstituted 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 **half** of this solution in up to 50 mL with sodium chloride 0.9% for intravenous use. No other reconstituting solution should be used. The reconstituted 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.

# 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.

# Reconstituted solution for injection and infusion

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

# Incompatibilities

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 DOSAGE AND ADMINISTRATION Method of administration). The reconstituted solution should not be mixed or coadministered in the same infusion set with any other drug.

# Use in Children

NEXIUM IV should not be used in children since no data are available.

# Geriatrics

Dose adjustment is not required in the elderly.

# Hepatic insufficiency

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 PRECAUTIONS).

# **Renal insufficiency**

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.

# OVERDOSAGE

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.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

# PRESENTATION AND STORAGE CONDITIONS

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.

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

# Storage

Store below 25°C and protect from light.

# NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd ABN 54 009 682 311 Alma Road NORTH RYDE NSW 2113

# POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

# DATE OF APPROVAL

Date of TGA approval: 22 December 2010

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

# \*Please note changes in Product Information

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This document refers to the use of esomeprazole, amoxycillin and clarithromycin in combination for the healing of patients with duodenal ulcer associated with *Helicobacter pylori* and for the eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer. The components of this therapy are frequently used to treat other conditions. For information about the treatment of other conditions, refer to full Product Information for the appropriate component.



esomeprazole, amoxycillin, clarithromycin

**NEXIUM<sup>®</sup> Hp7<sup>®</sup>** (esomeprazole, amoxycillin, clarithromycin)

# **PRODUCT INFORMATION**

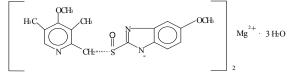
# NAME OF THE DRUG

 $\rm NEXIUM^{\$}$  Hp7<sup>®</sup> is a combination pack containing  $\rm NEXIUM^{\$}$  (esomeprazole) Tablets 20 mg,  $\rm AMOXIL^{\$}$  (amoxycillin) 500 mg capsules and KLACID<sup>®</sup> (clarithromycin) 500 mg tablets.

# NEXIUM

The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. The CAS number for esomeprazole is 217087-09-7.

The chemical structure for esomeprazole magnesium is:

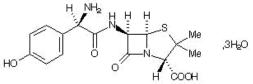


#### Amoxil

The chemical name of amoxycillin is (2S,5R,6R)-6-[(R)-2-amino-2-(4-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid.

The active ingredient in AMOXIL is amoxycillin trihydrate. The CAS number for amoxycillin trihydrate is 61336-70-7.

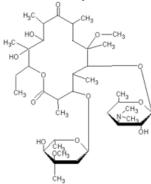
The chemical structure for amoxycillin trihydrate is:



# Klacid

The active ingredient in KLACID is clarithromycin. The CAS number for clarithromycin is 81103-11-9.

The chemical structure for clarithromycin is:



# DESCRIPTION

# NEXIUM

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

NEXIUM tablets contain esomeprazole magnesium trihydrate 22.3 mg as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, purified talc, triethyl citrate and sugar spheres (maize starch and sucrose). The tablet is coloured with titanium dioxide (CI77891), iron oxide yellow (CI77492) and iron oxide red (CI77491).

#### Amoxil

Amoxycillin trihydrate is a semisynthetic antibiotic and is a member of the penicillinase-stable group of penicillins derived from the penicillin nucleus, 6-aminopenicillanic acid. Amoxycillin trihydrate is a white or almost white, crystalline powder, which is slightly soluble in water and in ethanol (96%) and is practically insoluble in chloroform, in ether, and in fixed oils.

AMOXIL 500 mg capsule contains amoxycillin trihydrate equivalent to amoxycillin 500mg, plus magnesium stearate, gelatin, titanium dioxide (CI77891), iron oxide yellow (CI77492), erythrosine (CI45430), indigo carmine (CI73015) and Opacode A-R 9658 white.

#### Klacid

Clarithromycin is a semi-synthetic macrolide antibiotic. The chemical name of clarithromycin is 6-0-methylerythromycin A. Clarithromycin is a white to off-white crystalline powder, which is soluble in acetone, slightly soluble in methanol, ethanol and acetonitrile and practically insoluble in water.

KLACID tablets contain clarithromycin 500 mg, plus croscarmellose sodium, magnesium stearate, cellulose, povidone, silicon dioxide, hydroxypropylcellulose, purified talc, hypromellose, sorbitan monooleate, stearic acid, propylene glycol, sorbic acid and vanillin flavour, titanium dioxide (CI77891) and quinoline yellow (CI47005).

# PHARMACOLOGY

*Helicobacter pylori* (*H. pylori*) is a spiral, flagellated, Gram-negative rod, primarily colonising the antrum of the stomach, it congregates at, and around intercellular junctions. The natural habitat of *H.pylori* is the gastric mucosa, where the bacterium attaches itself via adhesion pedestals.

*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** and **DOSAGE AND 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 antisecretory treatment.

# Esomeprazole

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H<sup>+</sup>, K<sup>+</sup> 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 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 esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study, 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%

*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.

# Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

#### Microbiology

*In vitro* testing with omeprazole (mixed isomer) has shown that it has an  $MIC_{90}$  of 25 µg/mL against *H. pylori*. However, *in vivo* omeprazole and esomeprazole only suppress the organism without eradicating it.

#### Amoxycillin

Amoxycillin has been shown to have a bactericidal effect on *H. pylori in vitro*. Amoxycillin differs *in vitro* from benzylpenicillin in that it displays an enhanced bactericidal effect on Gram-negative bacteria. Like benzylpenicillin, amoxycillin is bactericidal against sensitive organisms during the stage of active multiplication. It is believed to act through the inhibition of biosynthesis of cell wall mucopeptide.

#### Clarithromycin

Clarithromycin is active *in vitro* and *in vivo* against *H. pylori*. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible organisms and inhibiting protein synthesis. The principal metabolite of clarithromycin in man is a microbiologically active metabolite, 14-hydroxy-clarithromycin.

#### Pharmacokinetics

A summary of the pharmacokinetic parameters for NEXIUM Hp7 are provided below.

#### Esomeprazole

#### Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets. 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 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 (see **Interactions with other Drugs**).

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.

# Amoxycillin and Clarithromycin

For further information regarding the pharmacokinetics of AMOXIL or KLACID, refer to the full Product Information for the appropriate component.

#### Amoxycillin

Amoxycillin is stable in the presence of gastric acid and is rapidly and well absorbed after oral administration, even in the presence of food. Amoxycillin diffuses rapidly into most body tissues and fluids, with the exception of brain and spinal fluid except when meninges are inflamed.

Amoxycillin has been shown to diffuse into sputum and saliva and is excreted mainly via the urine where it exists in a high concentration. The amount to be found in the bile is variable, depending on normal biliary secretory function.

Amoxycillin is excreted in the urine both unchanged and as penicilloic acid. About 75% of a 1 g dose is excreted in the urine in 6 hours in the presence of normal renal function (60% as amoxycillin and 15% as penicilloic acid). However, only 32% of a 3 g dose is excreted via the urine as the biologically active component in 8 hours (by which time most of the urinary excretion is complete). This proportional difference in the amount excreted from the different doses reflects a lack of linearity between doses and extent of absorption with a levelling off at higher doses of oral amoxycillin.

Excretion of amoxycillin can be delayed by concurrent administration of probenecid, thus prolonging its therapeutic effect.

Amoxycillin is not highly protein bound, being only 17% protein bound in serum as measured by ultrafiltration or equilibrium dialysis.

Orally administered doses of amoxycillin 500 mg resulted in average peak serum levels one to two hours after administration of 6.6 to 10.8 microgram/mL respectively. Detectable serum levels of amoxycillin are present eight hours after ingestion of a single dose.

#### Clarithromycin

Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of clarithromycin 250 mg tablets is  $\sim$ 50%.

Food intake half an hour before dosing increased both the rate and extent of clarithromycin absorption. In a study on the 500 mg tablets, the mean  $C_{max}$  and AUC values were 1.6±0.6 microgram/mL and 12.6±4.0 microgram.hour/mL (fasting) and 2.5±0.8 microgram/mL and 15.7±4.9 microgram.hour/mL (nonfasting), respectively. The consequences for the clinical efficacy of the increase in bioavailability caused by food are not known.

In studies of fasting healthy adults, peak serum concentrations were attained within two hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in two to three days and were approximately 2 to 3 microgram/mL with a 500 mg dose administered every 12 hours. The elimination half-life of clarithromycin was about five to seven hours with 500 mg administered every 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended dose of 500 mg administered every 12 hours, but is quite marked at higher doses. With a dosing of 500 mg every 12 hours, the peak steady-state concentration of 14-OH clarithromycin is up to 1 microgram/mL and its elimination half-life is about 7 hours. The steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. *In vitro* studies showed that protein binding of clarithromycin in human plasma averaged about 70% at clinically relevant concentrations of 0.45 to 4.5 microgram/mL.

After a dose of 500 mg every 12 hours, urinary excretion of unchanged parent drug is approximately 30%. The renal clearance of clarithromycin is however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin which accounts for an additional 10% to 15% of a 500 mg dose administered every 12 hours.

Clarithromycin is metabolised by cytochrome P450 (see Interactions with other Drugs).

# **CLINICAL TRIALS**

# Helicobacter pylori (H. 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 amoxycillin 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxycillin 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.

# INDICATION

Healing of duodenal ulcer associated with *Helicobacter pylori* and eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer.

# CONTRAINDICATIONS

Hypersensitivity to esomeprazole, substituted benzimidazoles,  $\beta$ -lactam antibiotics (e.g. penicillins, cephalosporins), clarithromycin, or any other constituents of the formulations.

History of an allergic reaction to penicillins or any macrolide antibiotic drugs.

Clarithromycin is contraindicated as concurrent therapy with astemizole, terfenadine, cisapride, pimozide, ergotamine or dihydroergotamine. (See **PRECAUTIONS, Interactions with other drugs**).

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (See **PRECAUTIONS, Interactions with other drugs**). Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

# PRECAUTIONS

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.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxycillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

# **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 NEXIUM Hp7 may alleviate symptoms and delay diagnosis.

# Anaphylaxis

Serious, and occasionally fatal, hypersensitivity (anaphylactoid) reactions have been reported in patients using  $\beta$ -lactam antibiotics and macrolide therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral administration. Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and amoxycillin and clarithromycin therapy discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

# Myasthenia gravis

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

#### Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxycillin and macrolides. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. *Clostridium difficile* associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibiotic agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

# Superinfection

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas* or *Candida*), the amoxycillin and clarithromycin components should be discontinued and/or appropriate therapy instituted.

# Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance of *H.pylori* eradication has not been comprehensively studied.

# Lymphatic Leukaemia

Amoxycillin should be given with caution to patients with lymphatic leukaemia, since they are especially susceptible to ampicillin induced skin rashes.

# Colchicine

There have been post marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

# **Special Patient Populations**

# CYP2C19 enzyme

# Esomeprazole

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.

# Elderly

# Esomeprazole

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

# Hepatic Insufficiency

# Esomeprazole

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 **DOSAGE AND ADMINISTRATION**).

# Clarithromycin

Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment.

# Impaired Renal Function

# Esomeprazole

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.

# Amoxycillin

Excretion of amoxycillin is delayed in patients with renal impairment, and depending on the degree of impairment, it may be necessary to reduce the total daily dosage (see **DOSAGE AND ADMINISTRATION**).

# Clarithromycin

The plasma levels, half-life,  $C_{max}$  and  $C_{min}$  for both clarithromycin and its 14-hydroxy metabolite are higher, and the AUC larger, in patients with renal impairment. Plasma levels and elimination half-life start increasing at creatinine clearance values of less than 30 mL/minute. In the presence of significant renal impairment, with or without co-existing hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate (see **DOSAGE AND ADMINISTRATION**).

# Carcinogenicity/Mutagenicity/Effects on Fertility

# Esomeprazole

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<sup>2</sup> basis) which ranged from 0.4 to 30-fold the maximum clinical dose. 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<sub>2</sub>-receptor antagonists and by partial fundectomy.

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*.

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.

# Clarithromycin

Clarithromycin gave negative results in a battery of mutagenicity studies with the exception of a positive result in an *in vitro* chromosome aberration assay. Long-term studies in animals have not been performed to assess carcinogenic potential.

# Use In pregnancy - Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM Hp7 should only be given to pregnant women if its use is considered essential.

For further information regarding the use of NEXIUM, AMOXIL and KLACID in pregnancy, refer to the full Product Information for the appropriate component.

# **Use In lactation**

NEXIUM Hp7 is not recommended for use during breastfeeding. It is not known if esomeprazole or its metabolites appear in human breast milk, although clarithromycin and amoxycillin may be excreted in breast milk. The safety of NEXIUM Hp7 for use during breast feeding of infants has not been established.

For further information regarding the use of NEXIUM, AMOXIL and KLACID in lactation, refer to the full Product Information for the appropriate component.

# Interactions with other drugs

# Cytochrome P450 Effects

Both esomeprazole and clarithromycin are metabolised in the liver via the cytochrome P450 system and may be expected to interact with other drugs metabolised by this system. Esomeprazole is metabolised by cytochrome P450 (CYP2C19 and CYP3A4), while clarithromycin is primarily metabolised by cytochrome P450 (CYP3A4).

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. This should be considered especially when prescribing esomeprazole for on demand therapy.

Esomeprazole has been shown to interact with diazepam, phenytoin, warfarin, citalopram, clomipramine, imipramine and atazanavir. Further

information is provided below. Details of other drugs metabolised via the cytochrome P450 system which have been shown not to be affected by concomitant esomeprazole treatment may be obtained from the NEXIUM Product Information.

There have been reports of clarithromycin producing elevations of serum levels of theophylline, phenytoin, cisapride, carbamazepine, cyclosporin, ergotamine, tacrolimus, HIV protease inhibitors and triazolam. Further information is provided below.

# Other drugs that effect esomeprazole, amoxycillin or clarithromycin

#### 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.

#### Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy adult volunteers led to increases in the mean steady state of clarithromycin  $C_{min}$  and AUC of 33 and 18% respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected.

# HIV Protease Inhibitors

*Ritonavir.* A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every twelve hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin  $C_{max}$  increased by 31%,  $C_{min}$  increased by 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered. For patients with a creatinine clearance of 30 to 60 mL/minute the dose of clarithromycin should be reduced by 50%. For patients with a creatinine clearance of <30 mL/minute the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 mg/day should not be co-administered with ritonavir.

# Probenecid

Probenecid decreases the renal tubular secretion of amoxycillin. Concurrent use with NEXIUM Hp7 may result in increased and prolonged blood levels of amoxycillin.

#### Others

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.

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

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.

# Fluoxetine

Fluoxetine is partially metabolised by the 2D6 isoform of P450. It is a weak inhibitor of CYP3A. Theoretically, this inhibition could result in possible elevation of clarithromycin levels.

# Efavirenz, nevirapine, rifabutin and rifampicin

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin and rifabutin may accelerate the metabolism of clarithromycin and thus lower the plasma levels of

clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

# Effects of esomeprazole, amoxycillin or clarithromycin on other drugs

# Allopurinol

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients. Similar reactions can be expected with the amoxycillin component of NEXIUM Hp7.

#### **Carbamazepine**

Single dose administration of clarithromycin has been shown to result in increased concentrations of carbamazepine. Blood level monitoring of carbamazepine should be considered if NEXIUM Hp7 is co-prescribed.

#### Cisapride and pimozide

Elevated cisapride levels have been reported in patients receiving concomitant clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see **CONTRAINDICATIONS**).

#### **Cilostazol**

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a crossover 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 **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.

# <u>Diazepam</u>

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam.

# **HIV Protease Inhibitors**

Atazanavir and nelfinavir. 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.

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

*Ritonavir.* Ritonavir produces a 77% increase in clarithromycin AUC but a 99.8% decrease in 14-hydroxy-clarithromycin AUC; no dosage

reduction of clarithromycin is recommended except in decreased renal function. Conversely, clarithromycin increases ritonavir AUC by 12%; no dosage adjustment of ritonavir is recommended.

*Indinavir*. The potential pharmacokinetic interaction between indinavir and clarithromycin was assessed in a three period, randomised, crossover, multiple dose study. Plasma concentration profiles of indinavir were consistently slightly higher in the presence of clarithromycin, although  $C_{max}$  changed minimally. Thus, clarithromycin has a modest inhibitory effect on indinavir metabolism. Results suggest that indinavir completely inhibits the oxidative metabolism of clarithromycin. The magnitude of the changes in the pharmacokinetics of clarithromycin and indinavir were not considered to be clinically significant, and co-administration of the drugs does not require dose adjustment.

Saquinavir. Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see **PRECAUTIONS, Interactions with other Medicines**).

*Zidovudine*. Simultaneous oral administration of clarithromycin and zidovudine in HIV infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can largely be avoided by staggering the doses of clarithromycin and zidovudine by at least two hours. This interaction does not appear to occur in paediatric HIV infected patients taking clarithromycin suspensions with zidovudine or didanosine.

#### Verapamil

Hypotension, bradyarrythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

#### HMG-CoA reductase inhibitors

Rhabdomyolysis coincident with the co-administration of clarithromycin and the HMG-CoA reductase inhibitors (e.g. lovastatin and simvastatin) has been rarely reported.

#### Oral contraceptives

In common with other broad spectrum antibiotics, amoxycillin may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

#### Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

There have been reports of clarithromycin interactions with phenytoin. Phenytoin is metabolised by the P450 system, although not by the 3A isoform. It is strongly recommended that plasma concentration of phenytoin be monitored if it is necessary to treat patients on phenytoin with NEXIUM Hp7.

# Antiarrythmics (quinidine or disopyramide)

There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

# Repaglinide

Clarithromycin may enhance and/or prolong the hypoglycaemic effect of repaglinide. In an interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a mechanism-based inhibitor of CYP3A4, increased the repaglinide AUC by 40% and C<sub>max</sub> by 67%, and increased the mean incremental AUC of serum insulin by 51% and the maximum concentration by 61%. The exact mechanism of this interaction is not clear.

#### **Tetracyclines**

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxycillin.

# Theophylline

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained release formulation was dosed at either 6.5 or 12 mg/kg, together with clarithromycin 250 or 500 mg every 12 hours), the steady state levels of C<sub>max</sub>, C<sub>min</sub> and AUC increased about 20%. Theophylline dosage may need to be reduced.

#### Oral anticoagulants

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.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin time should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxycillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxycillin.

# Ergotamine / dihydroergotamine

Post-marketing reports for clarithromycin indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischaemia of the extremities and other tissues, including the central nervous system. Hence, concomitant use of these medications is contraindicated (see **CONTRAINDICATIONS**).

# Terfenadine

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Concomitant use with this medication is therefore contraindicated (see **CONTRAINDICATIONS**).

#### **Colchicine**

Colchicine is a substrate for both CYP3A and the efflux transporter, Pglycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see **PRECAUTIONS**).

# Sildenafil, tadalafil and vardenafil

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are coadministered with clarithromycin.

#### **Tolterodine**

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.

# <u>Digoxin</u>

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (Pgp) by clarithromycin may lead to increased exposure

to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

#### 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 ketoconazole and itraconazole can decrease and the absorption of \*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).

#### CYP3A-based interactions

Cytochrome P450 3A (CYP3A) is the major isoform involved in clarithromycin metabolism. Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

There have been reports of clarithromycin interactions with cyclosporin, ergotamine and tacrolimus. Cyclosporin, ergotamine and tacrolimus are metabolised by CYP3A. As with other macrolide antibiotics, the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g. alprazolam, cilostazol, oral anticoagulants such as warfarin, ergot alkaloids, methylprednisolone, quinidine, triazolam, valproate, vinblastine, midazolam, disopyramide, phenytoin, digoxin, tacrolimus, cyclosporin, rifabutin and sildenafil) may be associated with elevations in serum levels of these drugs.

#### Triazolobenzodiazepines (e.g. triazolam and alprazolam) and related benzodiazepines (e.g. midazolam)

Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment.

The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines, which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and CNS effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

#### Food

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

Concomitant administration of food has no effect on the absorption of amoxycillin. The bioavailability of clarithromycin is increased in the presence of food, however, the clinical consequences of this effect are unknown.

# Laboratory tests

#### Amoxycillin

Oral administration of amoxycillin will result in high urine concentrations of amoxycillin. Since high urine concentrations of amoxycillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest<sup>®</sup>, Benedict's Solution or Fehling's Solution; it is recommended that glucose tests based on enzymatic

glucose oxidase reactions (such as  ${\rm Clinistix}^{\rm @}$  or  ${\rm Testape}^{\rm @})$  be used during treatment with NEXIUM Hp7.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated oestriol, oestriol glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxycillin.

# Esomeprazole

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 five days before CgA measurements.

# ADVERSE EFFECTS

*H. pylori* eradication therapy is generally well tolerated. Adverse events reported during clinical trials were not unexpected given the component substances. Common adverse reactions included diarrhoea and nausea.

Table 2Adverse events, regardless of causality, occurring at an<br/>incidence of greater than 0.5% in clinical trials, B13 and<br/>B14

	Esomeprazole (n=446)	Omeprazole (n=446)
Gastrointestinal system disorders		
Diarrhoea	21.5%	20.9%
Mouth dry	3.4%	1.2%
Flatulence	1.6%	1.1%
Nausea	1.3%	1.8%
Vomiting	1.1%	1.1%
Stomatitis	1.3%	0.9%
Abdominal pain	0.9%	0.9%
Dyspepsia	0.7%	0.2%
Tongue disorder	0.7%	0.7%
Special senses other, disorder		
Taste perversion	12.6%	15.2%
Central & peripheral nervous system disorders		
Headache	3.6%	2.2%
Liver and Biliary system disorders		
SGPT increased	1.8%	2.5%
SGOT increased	0.4%	1.1%
Bilirubinaemia	0.2%	1.2%
Respiratory system disorders		
Pharyngitis	1.1%	0.2%
Skin and appendages disorders		
Pruritus	0.4%	0.7%
Rash	0.2%	0.9%
Rash erythematous	0.7%	0.7%
Psychiatric disorders		
Insomnia	0.7%	0.2%
Haematologic disorders		
Anaemia	0.7%	1.2%
Thrombocytopenia	0%	0.7%
Urinary system disorders		
Haematuria	0.9%	0.7%

#### Esomeprazole

Esomeprazole is well tolerated. The following adverse drug reactions have been identified or suspected in the clinical trials programme and/or from post marketing use.

Adverse reactions within each body system are listed in descending order of frequency (Very common:  $\geq 10\%$ ; common:  $\geq 1\%$  and <10%; uncommon:  $\geq 0.1\%$  and <1%; rare  $\geq 0.01\%$  and <0.1%; very rare: <0.01%).

#### These include the following:

System Organ Class	Frequency	Event	
Blood and lymphatic system	Rare	leukopenia, thrombocytopenia	
disorders	Very rare	agranulocytosis, pancytopenia	
Immune system disorders	Rare	hypersensitivity reactions e.g. angioedema, anaphylactic reaction/shock	
Metabolism and nutrition	Uncommon	peripheral oedema	
disorders	Rare	hyponatraemia	
	Very rare	hypomagnesaemia	
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 disorders	Rare	blurred vision, visual accommodation disturbances	
Ear and labyrinth disorders	Uncommon	vertigo	
Respiratory, thoracic and mediastinal	Rare	bronchospasm	
Gastrointestinal disorders	Common	abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation	
	Uncommon	dry mouth	
	Rare	stomatitis, gastrointestinal candidiasis	
Hepatobiliary disorders	Uncommon	increased liver enzymes	
	Rare	hepatitis with or without jaundice	
	Very rare	hepatic failure, hepatic encephalopathy	
Skin and subcutaneous tissue	Uncommon	dermatitis, pruritus, urticaria, rash	
disorders	Rare	alopecia, photosensitivity	
	Very rare	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN	
Musculoskeletal, connective	Rare	arthralgia, myalgia	
tissue and bone disorders	Very rare	muscular weakness	
Renal and urinary disorders	Very rare	interstitial nephritis	
Reproductive system and breast disorders	Very rare	gynaecomastia	
General disorders	Rare	malaise, hyperhidrosis	

Adverse reactions that have been observed for the racemate (omeprazole) may occur with esomeprazole.

#### Amoxycillin

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins.

# Clarithromycin

Adverse events observed with clarithromycin are similar to those of other macrolide antibiotics.

For further information regarding the use of NEXIUM, AMOXIL and KLACID refer to the full Product Information for the appropriate component.

# DOSAGE AND ADMINISTRATION

The recommended dosage regimen of NEXIUM Hp7 is NEXIUM 20 mg twice daily, amoxycillin (AMOXIL) 1000 mg twice daily and clarithromycin (KLACID) 500 mg twice daily for 7 days.

Consult each individual Product Information documents for further advice on methods of administration.

# Use in children

NEXIUM Hp7 should not be used in children since no data is available.

# Geriatrics

Although this regimen has not been specifically studied in the elderly, dosage adjustment is not needed during therapy with the individual components. It is therefore unlikely to require dosage adjustment with NEXIUM Hp7.

# Renal Insufficiency

Patients with impaired kidney function require a reduced dose of both amoxycillin, and clarithromycin (see **PRECAUTIONS**).

In renal impairment the excretion of amoxycillin will be delayed and depending on the degree of impairment, it may be necessary to reduce the total daily dosage. In patients receiving peritoneal dialysis, the

maximum recommended dose is 500 mg/day. Amoxycillin may be removed from the circulation by haemodialysis.

# OVERDOSAGE

#### Esomeprazole

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively 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.

# Clarithromycin

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce pronounced gastrointestinal symptoms. Severe liver toxicity, including cholestatic jaundice may occur. There is no known antidote. Treatment consists of prompt elimination of the unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

#### Amoxycillin

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water/electrolyte imbalance should be treated symptomatically. During the administration of high doses of amoxycillin, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxycillin crystalluria. Amoxycillin can be removed from the circulation by haemodialysis.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

# PRESENTATION

NEXIUM Hp7 consists of:

14 light pink, oblong, biconvex, film coated NEXIUM Tablets 20 mg 28 red/yellow, hard, gelatin AMOXIL 500 mg capsules

# 14 pale yellow, smooth, film-coated ovaloid KLACID 500 mg tablets

# STORAGE

NEXIUM Hp7: Store below 25°C.

#### NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd ABN 54 009 682 311 Alma Road NORTH RYDE NSW 2113

#### POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine)

# DATE OF APPROVAL

Date of TGA approval: 22 December 2010

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

Amoxil is a registered trade mark of the GlaxoSmithKline group of companies.

Klacid is a registered trade mark of Abbott Australasia.

# \*Please note changes in Product Information

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