This document refers to the use of esomeprazole, amoxicillin 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.

AUSTRALIAN PRODUCT INFORMATION

NEXIUM® Hp7®

(esomeprazole magnesium trihydrate, amoxicillin trihydrate, clarithromycin)

1. NAME OF THE MEDICINE

NEXIUM Hp7 is a combination pack containing:

- esomeprazole magnesium trihydrate
- amoxicillin trihydrate
- clarithromycin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEXIUM

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. NEXIUM 20 mg tablets contain esomeprazole magnesium trihydrate 22.3 mg as the active ingredient.

Excipient with known effect: sugars.

AMOXIL

The active ingredient in AMOXIL is amoxicillin trihydrate. AMOXIL 500 mg capsule contains amoxicillin trihydrate equivalent to amoxicillin 500 mg.

KLACID

The active ingredient in KLACID is clarithromycin. KLACID tablets contain clarithromycin 500 mg.

Excipient with known effect: sorbates.

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

3. PHARMACEUTICAL FORM

NEXIUM Hp7 consists of:

- NEXIUM 20 mg enteric coated tablets which are light pink, oblong, biconvex, film-coated tablets
- AMOXIL 500 mg capsules which are red/yellow, hard, gelatin capsules
- KLACID 500 mg tablets which are pale yellow, film-coated ovaloid tablets

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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

Use in children

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

Use in the elderly

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.

Use in renal impairment

Patients with impaired kidney function require a reduced dose of both amoxicillin, and clarithromycin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In renal impairment, the excretion of amoxicillin 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. Amoxicillin may be removed from the circulation by haemodialysis.

4.3 CONTRAINDICATIONS

Hypersensitivity to esomeprazole, substituted benzimidazoles, β-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, domperidone and pimozide as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant administration of clarithromycin with lovastatin or simvastatin is also contraindicated due to the increased risk of myopathy, including rhabdomyolysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant administration of clarithromycin and lomitapide is contraindicated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of QT interval).

Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant administration of clarithromycin with ticagrelor or ranolazine is contraindicated.

Esomeprazole, like other proton pump inhibitors, should not be administered with atazanavir (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Concomitant administration of clarithromycin and oral midazolam is contraindicated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, in hospitalised patients, possibly also *Clostridioides difficile*.

Adequate fluid intake and urinary output must be maintained in patients receiving high doses of amoxicillin.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin 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.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue NEXIUM Hp7 if acute tubulointerstitial nephritis develops.

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 (including anaphylaxis, anaphylactoid and severe cutaneous reactions) have been reported in patients using β-lactam antibiotics and

macrolide therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. 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 amoxicillin 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after administration of amoxicillin) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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 amoxicillin 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). If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further. 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), 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 amoxicillin 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. Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

Lymphatic leukaemia

Amoxicillin 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. Concomitant administration of clarithromycin and colchicine is contraindicated (see Section 4.3 CONTRAINDICATIONS and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cardiovascular events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including clarithromycin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmia (including torsades de pointes), clarithromycin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.

- Clarithromycin must not be given to patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia (see Section 4.3 CONTRAINDICATIONS).

- Patients concomitantly taking other medicinal products associated with QT prolongation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

- Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide and terfenadine is contraindicated (see Section 4.3 CONTRAINDICATIONS).

- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see Section 4.3 CONTRAINDICATIONS).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides, including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Triazolobenzodiazepines

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - *Triazolobenzodiazepines (e.g. triazolam and alprazolam) and related benzodiazepines (e.g. midazolam)*).

Ototoxic drugs

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

Pneumonia

In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity

These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas, and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reaction (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and Henoch-Schonlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Oral hypoglycaemic agents/insulin

Clarithromycin

The concomitant use of clarithromycin and oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Oral anticoagulants

Clarithromycin

There is a risk of serious haemorrhage and significant elevations in International Normalised Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, particularly to patients at high risk of bleeding (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

HMG-CoA reductase inhibitors (statins)

Clarithromycin

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see Section 4.3 CONTRAINDICATIONS). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy.

Osteoporotic fractures

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

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

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

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

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most

patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

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

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

Special patient populations

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.

Use in hepatic impairment

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Clarithromycin

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment (see Section 4.3 CONTRAINDICATIONS).

Use in renal impairment

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.

Amoxicillin

Excretion of amoxicillin 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.9 OVERDOSE).

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Caution is advised in patients with moderate to severe renal insufficiency (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment (see Section 4.3 CONTRAINDICATIONS).

Use in the elderly

Esomeprazole

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

Paediatric use

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

Effects on laboratory tests

Amoxicillin

Oral administration of amoxicillin will result in high urine concentrations of amoxicillin. Since high urine concentrations of amoxicillin may result in false positive reactions when testing for the presence of glucose in urine using

Clinitest®, Benedict's Solution or Fehling's Solution; it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Testape®) 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 amoxicillin.

Esomeprazole

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

Clarithromycin

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, ciclosporin, ergotamine, tacrolimus, HIV protease inhibitors and triazolam. Further information is provided below.

Other drugs that effect esomeprazole, amoxicillin 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. Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see *Atazanavir* and *Saquinavir* below).

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with NEXIUM Hp7 may result in increased and prolonged blood levels of amoxicillin.

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 that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased

owing to the inhibition of CYP3A by clarithromycin (see also the relevant Product Information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

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, rifapentine and rifampicin

Strong inducers of the cytochrome P450 metabolism system (such as efavirenz, nevirapine, rifampicin, rifapentine 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.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin should be considered for the treatment of MAC.

Clopidogrel

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

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

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

Effects of esomeprazole, amoxicillin 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 amoxicillin 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, domperidone, pimozide, terfenadine and astemizole

Elevated levels of these drugs have been reported in patients receiving concomitant clarithromycin or another macrolide antibiotic. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. The concurrent use of macrolide antibiotics, including clarithromycin, with these drugs is contraindicated because of the potential for this interaction (see Section 4.3 CONTRAINDICATIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

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

Diazepam

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

Methotrexate

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

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Tacrolimus

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

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 <30mL/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, cross-over, 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Calcium channel blockers

Acute kidney injury has been reported in patients using clarithromycin and calcium channel blockers metabolised by CYP3A4 (e.g. verapamil, amlodipine, diltiazem), although causal association cannot be established. Most of the cases involved elderly patients 65 years of age or older.

Additionally, caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolised by CYP3A4 due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

HMG-CoA reductase inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolised by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis (see Section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered. Patients should be monitored for signs and symptoms of myopathy.

Oral contraceptives

In common with other broad spectrum antibiotics, amoxicillin 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.

Sodium valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A (e.g. phenytoin and sodium valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

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.

There have been post-marketing reports of hypoglycaemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Hydroxychloroquine and chloroquine

Clarithromycin should be used with caution in patients receiving these medicines. These medicines are known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

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_{max} 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 amoxicillin.

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_{max}, C_{min} and AUC increased about 20%. Theophylline dosage may need to be reduced.

Oral hypoglycaemic agents/insulin

With certain hypoglycaemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 INR in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or INR should be carefully monitored with the addition or withdrawal of amoxicillin.

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 Section 4.3 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 Section 4.3 CONTRAINDICATIONS).

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are administered together, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Concomitant use of clarithromycin and colchicine is contraindicated (see Section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Digoxin

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (P-gp) 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 and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

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.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isoenzyme (not a comprehensive list): alprazolam, astemizole, carbamazepine, cilostazol, cisapride, corticosteroids (e.g. methylprednisolone), ciclosporin, disopyramide, domperidone, ergot alkaloids, ibrutinib, ivabradine, lomitapide, lovastatin, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the CYP450 system include phenytoin, theophylline and sodium valproate.

Direct acting oral anticoagulants (DOACs)

The DOACs dabigatran and edoxaban are substrates for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents, particularly to patients at high risk of bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Erythromycin has been reported to decrease clearance of triazolam and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines. Concomitant administration of oral midazolam and clarithromycin is contraindicated. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration.

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.

Oral midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated.

Aminoglycosides

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 amoxicillin. The bioavailability of clarithromycin is increased in the presence of food, however, the clinical consequences of this effect are unknown.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Esomeprazole

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

Studies in rats have not shown any evidence of effects on fertility or reproductive performance following daily oral dosing up to 150 mg/kg/day in females (1.4-fold the maximum recommended human dose (MRHD) based on body surface area), and up to 500 mg/kg/day in males (5-fold the MRHD on a body surface area basis).

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.

The safety of clarithromycin for use in pregnancy has not yet been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

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 amoxicillin may be excreted in breast milk. Clarithromycin and other macrolides are excreted in human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 1 Adverse events, regardless of causality, occurring at an incidence of greater than 0.5% in clinical trials, B13 and 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		
Dysgeusia	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%

Table 1 Adverse events, regardless of causality, occurring at an incidence of greater than 0.5% in clinical trials, B13 and B14.

	Esomeprazole (n=446)	Omeprazole (n=446)
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: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Table 2 Esomeprazole adverse drug reactions – Clinical trials data and/or post-marketing experience

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Rare	leukopenia, thrombocytopenia
	Very rare	agranulocytosis, pancytopenia
Immune system disorders	Rare	hypersensitivity reactions (e.g. angioedema, anaphylactic reaction/shock)
Metabolism and nutrition disorders	Uncommon	peripheral oedema
	Rare	hyponatraemia
	Very rare	hypomagnesaemia; hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia
Psychiatric disorders	Uncommon	insomnia
	Rare	agitation, confusion, depression
	Very rare	aggression, hallucination

System Organ Class	Frequency	Event
Nervous system disorders	Common	headache
	Uncommon	dizziness, paraesthesia, somnolence
	Rare	dysgeusia
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
	Very Rare	microscopic colitis
Hepatobiliary disorders	Uncommon	increased liver enzymes
	Rare	hepatitis with or without jaundice
	Very rare	hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders	Uncommon	dermatitis, pruritus, urticaria, rash
	Rare	alopecia, photosensitivity
	Very rare	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
	Not known	subacute cutaneous lupus erythematosus (SCLE)
Musculoskeletal, connective tissue and bone disorders	Rare	arthralgia, myalgia
	Very rare	muscular weakness
Renal and urinary disorders	Very rare	Tubulointerstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders	Very rare	gynaecomastia
General disorders	Rare	malaise, hyperhidrosis

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

Amoxicillin

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.

The following adverse reactions have been reported as associated with the use of amoxicillin:

Cardiac disorders*:* Kounis syndrome: not known.

Infections and infestations: Mucocutaneous candidiasis has been reported very rarely.

Gastrointestinal: Nausea, vomiting, diarrhoea. Intestinal candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely. Black hairy tongue has been reported very rarely. Drug-induced enterocolitis syndrome: not known. (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Skin and subcutaneous tissue disorders*:* Linear IgA disease: not known.

Hypersensitivity reactions: Erythematous maculopapular rash, pruritus and urticaria have been reported occasionally. Rarely, skin reactions such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity vasculitis and interstitial nephritis have been reported rarely.

Whenever such reactions occur, amoxicillin should be discontinued (note: urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids). Anaphylaxis is the most serious reaction experienced (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Liver: A moderate rise in AST and/or ALT has occasionally been noted, but the significance of this finding is unknown. As with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been reported rarely.

Haemic and lymphatic systems: Reactions such as anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia and leukopenia (including severe neutropenia or agranulocytosis) have been reported during therapy with other penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Prolongation of bleeding time and prothrombin time have also been reported rarely.

Renal and urinary tract disorders: Interstitial nephritis. Crystalluria (including acute renal injury): not known (see Section 4.9 OVERDOSE).

CNS effects: CNS effects have been seen rarely. They include aseptic meningitis, hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Miscellaneous: Superficial tooth discolouration has been reported very rarely in children.

Clarithromycin

Adverse events observed with clarithromycin are similar to those of other macrolide antibiotics. Adverse events have been reported during post-approval use of clarithromycin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to clarithromycin exposure.

Table 3 Clarithromycin adverse events – Post-marketing experience

Body System	Adverse Reaction
Body as a whole	anaphylaxis, abdominal pain, asthenia, hypersensitivity, fever, headache, angioedema, chills, fatigue
Skin and skin structure	Severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, urticaria, rash, hyperhidrosis, pruritus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Henoch-Schonlein purpura
Central nervous system	anxiety, insomnia, somnolence, hallucinations, confusion, psychotic disorders, vertigo, dizziness, dream abnormality, tinnitus, disorientation, depersonalisation, nervousness, hyperkinesia, depression, paraesthesia, mania. There have been rare reports of convulsions.
Haematopoietic & lymphatic system	decreased white blood cell counts, decreased platelet counts, thrombocytopenia, thrombocythemia, leukopenia, agranulocytosis
Metabolic & nutritional	increased serum creatinine, increased gamma glutamyl transferase (GGT), hypoglycaemia[1], anorexia, decreased appetite
Special senses	hearing disturbances, dysgeusia, parosmia (smell perversion), ageusia, anosmia otitis media, deafness, taste perversion
Digestive system	dry mouth, tongue discolouration, glossitis, stomatitis, diarrhoea, nausea, vomiting, liver abnormalities, tooth discolouration, dyspepsia, enteritis, abdominal distension, eructation, flatulence, gastritis. There have been rare reports of pancreatitis.
Respiratory system	dyspnoea
Urogenital system	dysuria, renal failure, isolated cases of increased serum creatinine have been reported but an association has not been established. There have been reports of interstitial nephritis coincident with clarithromycin use.
Cardiac system[2]	torsade de pointes, electrocardiogram QT prolonged, ventricular tachycardia, ventricular fibrillation, palpitations

Body System	Adverse Reaction
Hepatobiliary system[3]	hepatic failure, hepatitis, hepatitis cholestatic, jaundice cholestatic, jaundice hepatocellular, cholestasis, hepatic function abnormal
Musculoskeletal and connective tissue disorders[4]	myalgia, rhabdomyolysis, myopathy, muscle spasms
Infections and infestations	pseudomembranous colitis, erysipelas, erythrasma, candidiasis, vaginal infection
Vascular disorders	haemorrhage
Investigations	International Normalised Ratio (INR) increased, prothrombin time prolonged, urine colour abnormal

1. There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.
2. As with other macrolides, QT prolongation, ventricular tachycardia and torsades de points have rarely been reported with clarithromycin.
3. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.
4. In some reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Reporting suspected adverse effects

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

4.9 OVERDOSE

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. One patient who had a history of bipolar disorder ingested eight grams

of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.

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.

Amoxicillin

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 amoxicillin, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria. Amoxicillin can be removed from the circulation by haemodialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nexium

NEXIUM is a proton pump inhibitor.

Amoxil

Amoxicillin trihydrate is a semisynthetic antibiotic and is a member of the penicillinase-stable group of penicillins derived from the penicillin nucleus, 6-aminopenicillanic acid.

Klacid

Clarithromycin is a semi-synthetic macrolide antibiotic.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of

peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Esomeprazole

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

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+ ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg 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 4 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	*Study drug*	*8 hours*	*12 hours*	*16 hours*
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%

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.

Amoxicillin

Amoxicillin has been shown to have a bactericidal effect on *H. pylori in vitro*. Amoxicillin differs *in vitro* from benzylpenicillin in that it displays an enhanced bactericidal effect on Gram-negative bacteria. Like benzylpenicillin, amoxicillin 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.

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 amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven-day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven-day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

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

5.2 PHARMACOKINETIC PROPERTIES

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Amoxicillin and clarithromycin

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

Amoxicillin

Absorption

Amoxicillin is stable in the presence of gastric acid and is rapidly and well absorbed after oral administration, even in the presence of food.

Orally administered doses of amoxicillin 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 amoxicillin are present eight hours after ingestion of a single dose.

Distribution

Amoxicillin diffuses rapidly into most body tissues and fluids, with the exception of brain and spinal fluid except when meninges are inflamed. Amoxicillin 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.

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

Excretion

Amoxicillin 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 amoxicillin 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 amoxicillin.

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

Clarithromycin

Absorption

Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of clarithromycin 250 mg tablets is ~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 (non-fasting), 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.

Distribution

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.

Metabolism

Clarithromycin is metabolised by cytochrome P450 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

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

Carcinogenicity

Esomeprazole

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

gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NEXIUM

NEXIUM tablets contain the following inactive ingredients: glyceryl monostearate, hyprolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, 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

AMOXIL 500 mg capsules contain the following inactive ingredients: magnesium stearate, purified talc, gelatin, titanium dioxide (CI77891), iron oxide yellow (CI77492), erythrosine (CI45430), indigo carmine (CI73015) and Tek Product- Tek Print SW-0012- White Ink.

KLACID

KLACID 500 mg tablets contain the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, hyprolose, purified talc, hypromellose, sorbitan mono-oleate, stearic acid, propylene glycol, sorbic acid and vanillin flavour, titanium dioxide (CI77891) and quinoline yellow (CI47005).

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in a dry place. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM® Hp7® is a combination pack containing 14 NEXIUM® (esomeprazole) 20 mg tablets, 28 AMOXIL® (amoxicillin) 500 mg capsules and 14 KLACID® (clarithromycin) 500 mg tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

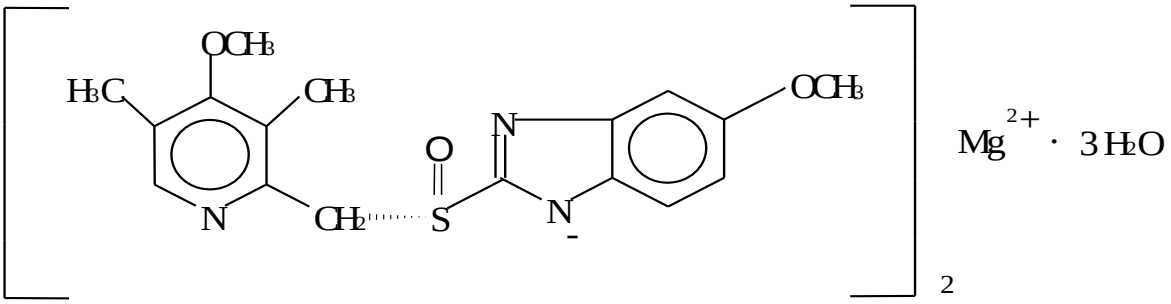
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

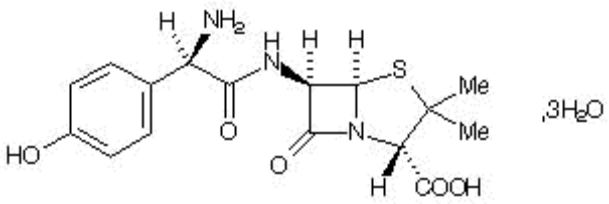
The chemical structure for esomeprazole magnesium trihydrate is:



Amoxil

The chemical name of amoxicillin 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. Amoxicillin 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.

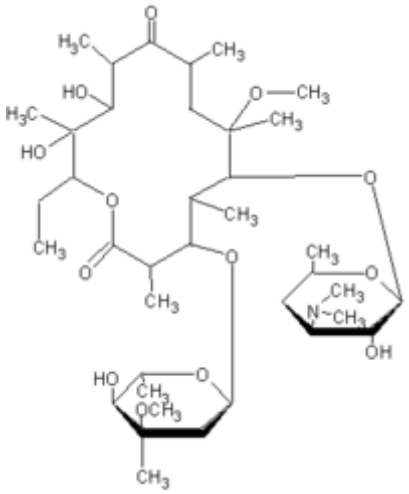
The chemical structure for amoxicillin trihydrate is:



Klacid

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.

The chemical structure for clarithromycin is:



CAS number

The CAS number for esomeprazole is 217087-09-7.

The CAS number for amoxicillin trihydrate is 61336-70-7.

The CAS number for clarithromycin is 81103-11-9.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

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

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

24 December 2024

Summary table of changes

Section changed	Summary of new information
4.4	Addition of a paragraph under Acute tubulointerstial nephritis requested by TGA on 27 Sep 2024

Section changed	Summary of new information
4.8	Update of text under Renal and urinary disorders requested by TGA on 27 Sep 2024

Both NEXIUM® and NEXIUM®Hp7® are registered trade marks of the AstraZeneca group of companies.
AMOXIL® is a registered trade mark of the Aspen Global Inc. group of companies.
KLACID® is a registered trade mark of Viatris Pty Ltd.

VV-RIM-01376752 v34.0