**For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only**

# NEXPRO HP Kit

## 1. Generic Name

Combipack of Clarithromycin Tablets, Esomeprazole Gastro-Resistant Tablets and Amoxicillin Tablets

## 2. Qualitative and quantitative composition

Each strip contains:

### A. Clarithromycin Tablets I.P. 2 Tablets

Each film coated tablet contains:

Clarithromycin I.P...……500 mg

Excipients……..…q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Pregelatinised Starch, Polyvinyl Pyrrolidone, Ac-di-sol, Talcum, Starch, Colloidal Silicon Dioxide, Stearic acid, Magnesium Stearate, HPMC, Isopropyl Alcohol, Methylene Chloride, PEG 6000 and Titanium Dioxide.

### B. Esomeprazole Gastro-resistant Tablets I.P. 2 Tablets

Each gastro-resistant tablet contains:

Esomeprazole Magnesium Trihydrate I.P. equivalent to Esomeprazole…..40 mg

Excipients……..…q.s.

Colours: Red Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Mannitol, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Sodium Carbonate, Sodium Stearyl Fumarate, Microcrystalline Cellulose, Crospovidone, Talcum, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Red Oxide of Iron, PEG 6000.

### C. Amoxicillin Tablets U.S.P. 2 Tablets

Each film tablet contains:

Amoxycillin Trihydrate I.P. equivalent to Amoxycillin…..750 mg

Excipients……..…q.s.

Colours: Sunset Yellow FCF and Titanium Dioxide I.P.

The excipients used are Starch, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, PEG 6000, Titanium Dioxide, Methylene Chloride, HPMC and Sunset Yellow

## 3. Dosage form and strength

Clarithromycin 500 mg Film coated tablet

Amoxicillin 750 mg Film coated tablet

Esomeprazole 40 mg Gastro-resistant tablet

## 4. Clinical particulars

### 4.1 Therapeutic indication

It is indicated for healing of duodenal ulcer associated with H.Pylori and eradication of H.Pylori in patients with active or healed peptic ulcer.

### 4.2 Posology and method of administration

The recommended dosage for NEXPRO HP KIT is one tablet of each clarithromycin, esomeprazole and amoxicillin twice daily for 7 days.

Dosage in renal functional impairment:

The maximum recommended dosages should be reduced proportionately to renal impairment. In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e. 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

Dosage adjustment is also required for amoxicillin as mentioned below:

Glomerular filtration rate >30ml/min: No adjustment necessary.

Glomerular filtration rate 10-30ml/min: Amoxicillin. max.500mg b.d

Glomerular filtration rate<10ml/min: Amoxicillin. Max. 500mg/day

Method of administration

Esomeprazole:

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed. For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested.

Clarithromycin:

Clarithromycin film-coated tablets may be given irrespective of food intake. Food does not affect the extent of bioavailability. Food does only slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite.

Amoxicillin

Amoxicillin Heumann film-coated tablets should be swallowed whole with sufficient liquids (e.g. a glass of water). Taking it independent of meals or during a meal does not affect the efficacy of amoxicillin.

## 4.3 Contraindications

### Amoxicillin

Hypersensitivity to the active substance, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. acephalosporin, carbapenem or monobactam).

### Clarithromycin

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs or any of the excipients.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine.

Clarithromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CP3A4, (lovastatin or simvastatin), due to the risk of myopathy, including rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment.

Colchicine is contraindicated in patients with renal or hepatic impairment who are taking P-glycoprotein or a strong CYP3A4 inhibitor.

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

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

### Esomeprazole

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients.

Esomeprazole should not be used concomitantly with nelfinavir.

## 4.4 Special warnings and precautions for use

### Amoxicillin

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders.

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis. This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.

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.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Crystalluria

In patients with reduced urine output, crystalluria 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.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

**Clarithromycin**

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic function and moderate to severe renal impairment.

Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Prolonged or repeated use of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If superinfection occurs, clarithromycin should be discontinued and appropriate therapy instituted. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

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

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. If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam.

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.

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation. Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.

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* (erythrasma), acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, 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.

HMG-CoA reductase inhibitors: Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration which increases the risk of myopathy, including rhabdomyolysis. 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. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

Oral hypoglycaemic agents/Insulin: 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.

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized 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.

Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms.

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**Esomeprazole**

In 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.

Long term use

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On demand treatment

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

*Helicobacter pylori eradication*

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.

Gastrointestinal infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Absorption of vitamin B12

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. 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. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

## 4.5 Drugs interactions

**Amoxicillin**

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin.

Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

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

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

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

**Clarithromycin**

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine

Clarithromycin has been reported to elevate plasma levels of cisapride when taken concomitantly. Increased levels of these drugs 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 concurrently

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

HMG-CoA reductase inhibitors

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated.

**Effect of other medicinal products on clarithromycin**

Products that are inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy. Furthermore it might be necessary to monitor the plasma levels of the CYP3A4 inducer, which could be increased owing to the inhibition of CYP3A4 by clarithromycin. 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.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required:

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine 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-OHclarithromycin, 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.

Fluconazole

Concomitant administration of fluconazole 200mg daily and clarithromycin 500mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration ($C_{min}$) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14(R)-hydroxyclarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200mg every eight hours and clarithromycin 500mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin $C_{max}$ increased by 31%, $C_{min}$ increased 182% and AUC increased by 77% with concomitant administration of ritonavir.

An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. 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, such as clarithromycin immediate release tablets, or clarithromycin sachet, or clarithromycin paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors

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.

Effects of clarithromycin on other medicinal products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized 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 metabolized by this enzyme.

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

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketing reports of torsade 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 concentrations of these medications should also be monitored during clarithromycin therapy.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin.

Dose reduction may need to be considered.

Oral anticoagulants (e.g., warfarin, acenocoumarol)

In isolated cases, patients receiving combination therapy with clarithromycin and oral anticoagulants may experience increased pharmacologic effects and even toxic effects of these drugs. International normalized ratio (INR) or Prothrombin times should be carefully monitored while patients are simultaneously receiving clarithromycin and oral anticoagulants.

Sildenafil, tadalafil, and vardenafil

Each of these phosphodiesterase inhibitors is metabolized, 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 co-administered 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.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. 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 metabolised by CYP3A (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (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.

Omeprazole

Clarithromycin (500mg every 8 hours) was given in combination with omeprazole (40mg daily) to healthy adult subjects.

The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 increased by 30%, 89% and 34% respectively, when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.

***Other Interactions***

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (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.

Digoxin

Digoxin is a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of 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 concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Due to reduced gastrointestinal absorption of zidovudine in the presence of clarithromycin, reduced serum levels of zidovudine were observed in adults during concomitant therapy with clarithromycin and zidovudine. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, patients should observe a 4-hour interval between taking these two drugs. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and valproate

There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolized by CYP3A, including phenytoin and valproate. Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased concentrations have been reported.

***Bidirectional pharmacokinetic interactions***

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500mg twice daily) with atazanavir (400mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14(R)-hydroxy-clarithromycin, with a 28% increase in the AUC of atazanavir. 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, such as clarithromycin immediate release tablets, or clarithromycin sachet, or clarithromycin paediatric suspensions (not

all presentations may be marketed).

Doses of clarithromycin greater than 1000mg per day should not be co-administered with protease inhibitors.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional 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.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve (AUC) and maximum concentration ($C_{max}$) values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and $C_{max}$ values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule.

Observations from drug interaction studies done with unboosted saquinavir may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Verapamil

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

**Esomeprazole**

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. 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 protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, $C_{max}$ and $C_{min}$). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg

qd) reduced mean nelfinavir AUC, $C_{max}$ and $C_{min}$ by 36–39 % and mean AUC, $C_{max}$ and $C_{min}$ for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

*Methotrexate*

When given together with PPIs, 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.

*Tacrolimus*

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

*Medicinal products with pH dependent absorption*

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib 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).

Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., 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.

*Diazepam*

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

*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.

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) $C_{max}$ and AUCτ by 15% and 41%, respectively.

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.

*Cisapride*

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) 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.

*Warfarin*

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel

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

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

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

*Investigated medicinal products with no clinically relevant interaction*

*Amoxicillin and quinidine*

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

*Naproxen or rofecoxib*

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

*Medicinal products which inhibit CYP2C19 and/or CYP3A4*

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

*Medicinal products which induce CYP2C19 and/or CYP3A4*

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.

*Paediatric population*

Interaction studies have only been performed in adults.

**4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

**Amoxicillin**

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

**Clarithromycin**

Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. Clarithromycin is excreted into human breast milk.

**Esomeprazole**

Pregnancy

Clinical data on exposed pregnancies with esomeparazole are insufficient. With the racemic

mixture omeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects.

Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Breast-feeding

It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

## 4.7 Effects on ability to drive and use machines

### Amoxicillin

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

### Clarithromycin

There are no data on the effect of this product on the driving ability. When driving or using machines, one should take into account that dizziness, vertigo, confusion and disorientation may occur.

### Esomeprazole

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported. If affected patients should not drive or use machines.

## 4.8 Undesirable effects

### Amoxicillin

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash.

The ADRs derived from clinical studies and post- marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

| | |
|---|---|
| **Infections and infestations** | |
| Very Rare | Mucocutaneous candidiasis |
| **Blood and lymphatic system disorders** | |
| Very rare | Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia.<br>Prolongation of bleeding time and prothrombin time. |
| **Immune system disorders** | |
| Very rare | Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis. |
| Not known | Jarisch-Herxheimer reaction. |
| **Nervous system disorders** | |
| Very rare | Hyperkinesia, dizziness and convulsions. |
| **Gastrointestinal disorders** | |
| *Clinical Trial Data* | |
| **Common* | Diarrhoea and nausea |
| **Uncommon* | Vomiting |
| *Post-marketing Data* | |
| Very Rare | Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis).<br>Black hairy tongue<br>Superficial tooth discolouration[#] |
| **Hepatobiliary disorders** | |
| Very Rare | Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT. |

| | |
|---|---|
| **Skin and subcutaneous tissue disorders** | |
| *Clinical Trial Data* | |
| *Common | Skin rash |
| *Uncommon | Urticaria and pruritus |
| *Post-marketing Data* | |
| Very rare | Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). |
| **Renal and urinary tract disorders** | |
| Very rare | Interstitial nephritis<br>Crystalluria |
| *The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.<br>#Superficial tooth discolouration has been reported in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing. | |

**Clarithromycin**

**a. Summary of the safety profile**

The most frequent and common adverse reactions related to clarithromycin for both adult and paediatric populations are abdominal pain, nausea, vomiting and taste perversion.

These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

**b. Tabulated summary of adverse reactions**

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended- release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

| System Organ Class | Very common (≥1/10) | Common (≥1/100, <1/10) | Uncommon (≥1/1000, <1/100) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|
| Infections and infestations | | | cellulitis, gastroenteritis, candidiasis, infection, vaginal infection | Pseudomembranous colitis, erysipelas, erythrasma |
| Blood and the lymphatic system disorders | | | leukopenia, neutropenia, eosinophilia, thrombocythaemia | agranulocytosis, thrombocytopenia |
| Immune system disorders | | | Anaphylactoid reaction, hypersensitivity | anaphylactic reaction |
| Psychiatric disorders | | Insomnia | Anxiety, nervousness, screaming | psychiatric disorder, confusional state, depression, hallucination, disorientation, depersonalisation, abnormal dreams and confusion |
| Metabolism and nutrition disorders | | | anorexia, decreased appetite | Hypoglycaemia[6] |
| Vascular disorders | | | vasodilation | Heamorrhage[9] |
| Respiratory, thoracic and mediastinal disorders | | | Asthma[1], epitaxis[2], pulmonary embolism[1] | |
| General disorders and administration site conditions | Injection site phlebitis [1] | injection site pain[1], injection site inflammation[1] | Pyrexia[3], asthenia, chest pain[4], chills[4], malaise[4], fatigue, thirst | |
| Nervous system disorders | | dysguesia, headache, taste perversion | Loss of consciousness[1], dyskinesia[1], tremor, dizziness, somnolence | convulsions, aguesia, parosmia, anosmia |
| Ear and labyrinth | | | vertigo, hearing impaired, tinnitus | Deafness |

| | | | | |
|---|---|---|---|---|
| disorders | | | | |
| Cardiac disorders | | | Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[8], extrasystoles[1], palpitations | Ventricular tachycardia[8], torsade de pointes[8] |
| Gastrointestinal disorders | | Nausea, diarrhoea[10], vomiting, abdominal pain, dyspepsia | Esophagitis, gastrooseophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distention, constipation, dry mouth, eructation, flatulence, gastrointestinal haemorrhage | pancreatitis acute; tongue discolouration, tooth discolouration |
| Hepato-biliary disorders | | liver function test abnormal | hepatitis, cholestasis, alanine aminotransferase increased, aspartate aminotransferase increased, gammaglutamyltransferase increased | fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic drugs |
| Skin and subcutaneous tissue disorders | | rash, hyperhidrosis | dermatitis bullous, dry skin, pruritus, urticaria, rash maculopapular | Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne |
| Musculoskeletal, connective tissue and bone disorders | | | muscle spams, musculoskeletal stiffness, myalgia | Rhabdomyolysis, myopathy, exacerbation of symptoms of myasthenia gravis |
| Renal and urinary disorders | | | blood creatinine increased, blood urea increased | |

| | | | | |
|---|---|---|---|---|
| Investigations | | albumin globulin ratio abnormal, alkaline phosphatase increased, blood lactate dehydrogenase increased | | International normalised ration increased, increased prothrombin time, urine colour abnormal |

[1] ADRs reported only for the Powder for Solution for Injection formulation

[2] ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5, 8, 10, 11, 12] See section a) above

[6, 7, 9] See section c) below

**c. Description of selected adverse reactions**

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

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.

A special attention to diarrhoea should be paid as Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

As with other macrolides, QT prolongation, ventricular tachycardia, and torsade de pointes have rarely been reported with clarithromycin Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

In some of the 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 elderly and/or patients with renal insufficiency, some with a fatal outcome.

There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

There have been post-marketing reports of drug interactions and central nervous system (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.

There is a risk of serious haemorrhage and significant elevations in 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.

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients.

**d. Paediatric populations**

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age.

Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

**e. Other special populations**

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1,000mg and 2,000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000mg and 2,000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1,000mg or 2,000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4,000mg daily for all parameters except White Blood Cell.

**Esomeprazole**

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the

safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

| **System Organ Class** | **Frequency** | **Undesirable Effect** |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Leukopenia, thrombocytopenia |
| | Very rare | Agranulocytosis, pancytopenia |
| Immune system disorders | Rare | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock |
| Metabolism and nutrition disorders | Uncommon | Peripheral oedema |
| | Rare | Hyponatraemia |
| | Not known | Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia. |
| Psychiatric disorders | Uncommon | Insomnia |
| | Rare | Agitation, confusion, depression |
| | Very rare | Aggression, hallucinations |
| Nervous system disorders | Common | Headache |
| | Uncommon | Dizziness, paraesthesia, somnolence |
| | Rare | Taste disturbance |
| Eye disorders | Rare | Blurred vision |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Rare | Bronchospasm |
| Gastrointestinal disorders | Common | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, |

| | | |
|---|---|---|
| | | fundic gland polyps (benign) |
| | Uncommon | Dry mouth |
| | Rare | Stomatitis, gastrointestinal candidiasis |
| | Not known | Microscopic colitis |
| Hepatobiliary disorders | Uncommon | Increased liver enzymes |
| | Rare | Hepatitis with or without jaundice |
| | Very rare | Hepatic failure, encephalopathy in patients with pre-existing liver disease |
| Skin and subcutaneous tissue disorders | Uncommon | Dermatitis, pruritus, rash, urticarial |
| | Rare | Alopecia, photosensitivity |
| | Very rare | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) |
| | Not known | Subacute cutaneous lupus erythematosus |
| Musculoskeletal and connective tissue disorders | Uncommon | Fracture of the hip, wrist or spine |
| | Rare | Arthralgia, myalgia |
| | Very rare | Muscular weakness |
| Renal and urinary disorders | Very rare | Interstitial nephritis; in some patients renal failure has been reported concomitantly, Acute kidney injury |
| Reproductive system and breast disorders | Very rare | Gynaecomastia |
| General disorders and administration site conditions | Rare | Malaise, increased sweating |

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting

## 4.9 Overdose

### Amoxicillin

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by haemodialysis.

### Clarithromycin

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

### Esomeprazole

There is very limited experience to date with deliberate overdose. 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 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.

# 5. Pharmacological properties

## 5.1 Pharmacodynamic properties

### Amoxicillin

**Pharmacotherapeutic group:** penicillins with extended spectrum

**ATC code:** J01CA04

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gramnegative bacteria.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

| **Organism** | **MIC breakpoint (mg/L)** | |
|---|---|---|
| | **Susceptible ≤** | **Resistant >** |
| Enterobacteriaceae | 8[1] | 8 |
| Staphylococcus spp. | Note[2] | Note[2] |
| *Enterococcus spp* | 4 | 8 |
| *Streptococcus groups A, B, C and G* | Note[4] | Note[4] |
| *Streptococcus pneumonia* | Note[5] | Note[5] |
| *Viridans group steprococci* | 0.5 | 2 |
| *Haemophilus influenzae* | 2[6] | 2[6] |
| *Moraxella catarrhalis Note Note* | Note[7] | Note[7] |
| *Neisseria meningitides* | 0.125 | 1 |
| *Gram positive anaerobes except Clostridium difficile* | 4 | 8 |
| *Gram negative anaerobes* | 0.5 | 2 |

| | | |
|---|---|---|
| *Helicobacter pylori* | 0.125[9] | 0.125[9] |
| *Pasteurella multocida* | 1 | 1 |
| *Non- species related breakpoints* | 2 | 8 |

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L

[2]Most staphylococci are penicillinase producers, which are resistant to amoxicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.

[3]Susceptibility to amoxicillin can be inferred from ampicillin

[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility.

[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicillin avoid oral treatment with amoxicillin. Susceptibility inferred from the MIC of ampicillin.

[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be reported resistant.

[7]Beta lactamase producers should be reported resistant

[8]Susceptibility to amoxicillin can be inferred from benzylpenicillin.

[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3or 4 doses daily (1.5 to 2 g/day).

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

| **In vitro susceptibility of micro-organisms to Amoxicillin** |
|---|
| **<u>Commonly Susceptible Species</u>** |
| <u>Gram-positive aerobes:</u> |
| *Enterococcus faecalis*<br>Beta-hemolytic streptococci (Groups A, B, C and G)<br>*Listeria monocytogenes* |

| ***Species for which acquired resistance may be a problem*** |
|---|
| Gram-negative aerobes:<br>*Escherichia coli*<br>*Haemophilus influenzae*<br>*Helicobacter pylori*<br>*Proteus mirabilis*<br>*Salmonella typhi*<br>*Salmonella paratyphi*<br>*Pasteurella multocida* |
| Gram-positive aerobes:<br>Coagulase negative staphylococcus<br>Staphylococcus aureus<br>Streptococcus pneumoniae<br>Viridans group streptococcus |
| Gram-positive anaerobes:<br>Clostridium spp. |
| Gram-negative anaerobes:<br>Fusobacterium spp. |
| Other:<br>*Borrelia burgdorferi* |
| **Inherently resistant organisms** |
| Gram-positive aerobes:<br>*Enterococcus faecium* |
| Gram-negative aerobes:<br>Acinetobacter spp.<br>Enterobacter spp.<br>Klebsiella spp.<br>Pseudomonas spp. |
| Gram-negative anaerobes:<br>Bacteroides spp. |
| Others: |

| |
|---|
| Chlamydia spp.<br>*Mycoplasma* spp.<br>*Legionella* spp. |
| †Natural intermediate susceptibility in the absence of acquired mechanism of resistance.<br>£Almost all *S.aureus* are resistant to amoxilcillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin. |

**Clarithromycin**

**Pharmacotherapeutic group:** Macrolides

**ATC code:** J01FA09

Mechanism of Action: Clarithromycin is a semi-synthetic derivative of erythromycin. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or twofold higher than the MICs of the parent compound, except for *Haemophilus influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae*; *Streptococcus agalactiae*; *Listeria monocytogenes*.

Gram-negative Bacteria: *Haemophilus influenza*; *Haemophilus parainfluenza*; *Moraxella (Branhamella) catarrhalis*; *Neisseria gonorrhoeae*; *Legionella pneumophila*; *Bordetella pertussis*; *Campylobacter jejuni*.

Mycoplasma: *Mycoplasma pneumoniae*; *Ureaplasma urealyticum*.

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Mycobacterium kansasii; Mycobacterium chelonae; Mycobacterium fortuitum; Mycobacterium intracellularis; Chlamydia pneumoniae*.

Anaerobes: *Clostridium perfringens*; Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes*.

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus agalactiae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae* and Campylobacter spp.

**Esomeprazole**

**Pharmacotherapeutic group:** Drugs for acid-related disorders proton pump inhibitors

**ATC code:** A02B C05

Esomeprazole is the *S*-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the *R*- and *S*-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action

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.

Pharmacodynamic effects

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 GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

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

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One weeks treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of H.pylori in approximately 90% of patients.

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.

In a randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomised to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of re-bleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of re-bleeding in the esomeprazole treated versus the placebo treated group was 7.7% vs 13.6%.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term 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 to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

Clinical efficacy

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

## 5.2 Pharmacokinetic properties

**Amoxicillin**

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration ($T_{max}$) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

| $C_{max}$ | $T_{max}$* | AUC $_{(0-24h)}$ | $T_{½}$ |
|---|---|---|---|
| (µg/ml) | (h) | (µg.h/ml) | (h) |
| 3.3 ± 1.12 | 1.5 (1.0-2.0) | 26.7 ± 4.56 | 1.36 ± 0.56 |
| *Median (range) | | | |

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as Cmax and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk.

Amoxicillin has been shown to cross the placental barrier.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Elimination

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24 hour period.

Concomitant use of probenecid delays amoxicillin excretion.

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults.

For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function.

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

**Clarithromycin**

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following in vitro and in vivo data are applicable to the modified-release formulation.

In vitro: Results of in vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70 % at concentrations of 0.45 - 4.5µg/mL. A decrease in binding to 41% at 45.0µg/mL suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of therapeutic drug levels.

In vivo: Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg

clarithromycin modified-release daily, the peak steady state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1.3 and 0.48µg/mL, respectively. When the dosage was increased to 1000mg daily, these steady-state values were 2.4µg/mL and 0.67µg/mL respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively.

The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

**Esomeprazole**

**Absorption**

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the *R*-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after 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% plasma protein bound.

Biotransformation

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). 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.

Elimination

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. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

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

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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.

Special patient populations

*Poor metabolisers*

Approximately 2.9 ±1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly 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 peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

*Gender*

Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration.

These findings have no implications for the posology of esomeprazole.

*Hepatic impairment*

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of 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.

*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.

*Elderly*

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

*Paediatric population*

*Adolescents 12-18 years:*

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration ($t_{max}$) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

## 6. Nonclinical properties

### Amoxicillin

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

**Clarithromycin**

In repeated dose studies, clarithromycin toxicity was related to dose and duration of treatment. The liver was the primary target organ in all species with hepatic lesions seen after 14 days in dogs and monkeys. Systemic exposure levels associated with this toxicity are not known but toxic mg/kg doses were higher than the dose recommended for patient treatment.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

No other toxicological findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

**Esomeprazole**

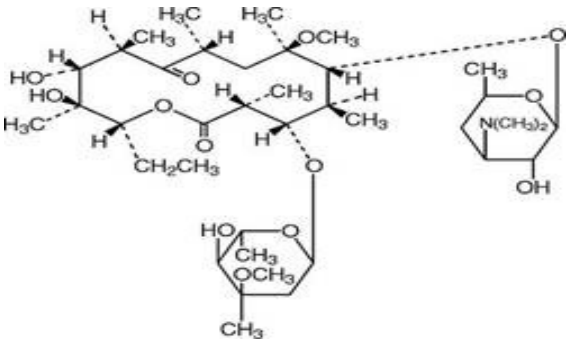
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

## 7. Description

**<u>Clarithromycin</u>**

Clarithromycin is 6-0-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:

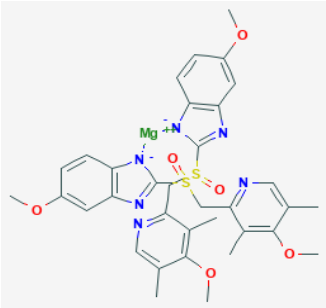


Clarithromycin is white to almost white, crystalline powder which is practically insoluble in water; soluble in acetone and dichloromethane; slightly soluble in methanol.

Clarithromycin tablets are white, caplet shape, one side score, other side plain & film coated tablets. The excipients used are Microcrystalline Cellulose, Pregelatinised Starch, Polyvinyl Pyrrolidone, Ac-di-sol, Talcum, Starch, Colloidal Silicon Dioxide, Stearic acid, Magnesium Stearate, HPMC, Isopropyl Alcohol, Methylene Chloride, PEG 6000 and Titanium Dioxide.

**Esomeprazole Magnesium Trihydrate**

Esomeprazole Magnesium Trihydrate is 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]benzimidazol-1-ide magnesium trihydrate. The molecular formula is $C_{34}H_{36}MgN_6O_6S_2$, and the molecular weight is 713.1 g/mol. The structural formula is:

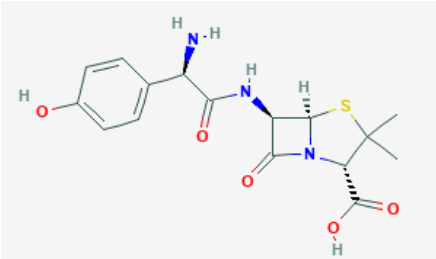


Esomeprazole Magnesium Trihydrate is white to off-white powder which is soluble in N,N-dimethyl formamide.

Esomeprazole Gastro-resistant Tablets are pinkish brown colour, round, biconvex, gastro-resistant tablets. The excipients used are Mannitol, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Sodium Carbonate, Sodium Stearyl Fumarate, Microcrystalline Cellulose, Crospovidone, Talcum, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Red Oxide of Iron, PEG 6000.

**Amoxicillin Trihydrate**

Amoxicillin trihydrate is (6R)-6-(α-4-hydroxyphenyl-D-glycylamino)penicillanic acid trihydrate. The molecular formula is $C_{16}H_{19}N_3O_5S,3H_2O$ and molecular weight of 365.4 g/mol. The chemical structure is:



Amoxicillin trihydrate is white or almost white crystalline powder which is slightly soluble in water; soluble in dilute solution of acids and of alkali hydroxides; practically insoluble in ethanol, in chloroform, in ether and in fixed oils.

Orange coloured, caplet shaped, biconvex, one side scored & film coated tablets. The excipients used are Starch, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, PEG 6000, Titanium Dioxide, Methylene Chloride, HPMC and Sunset Yellow.

## 8. Pharmaceutical particulars

### 8.1 Incompatibilities

Not applicable

### 8.2 Shelf-life

Do not use later than the date of expiry.

**8.3 Packaging information**

NEXPRO HP Kit is available as strip of 6 tablets.

**8.4 Storage and handing instructions**

Store at a temperature not exceeding 30°C, Protected from light and moisture.

Keep out of reach of children.

## 9. Patient counselling information

### Package leaflet: information for the patient

### NEXPRO HP KIT

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet?**

9.1.What NEXPRO HP KIT is and what it is used for

9.2.What you need to know before you take NEXPRO HP KIT

9.3.How to take NEXPRO HP KIT

9.4.Possible side effects of NEXPRO HP KIT

9.5.How to store NEXPRO HP KIT

9.6.Contents of the pack and other information

**9.1.What NEXPRO HP is and what it is used for**

NEXPRO HP KIT is a combipack of three different tablets which are Clarithromycin 500 mg Film coated tablet, Amoxicillin 750 mg Film coated tablet and Esomeprazole 40 mg Enteric coated tablet. NEXPRO HP KIT is used to treat and to prevent the stomach and peptic ulcers caused by bacteria known as Helicobacter pylori.

**9.2.What you need to know before you take NEXPRO HP**

**Do not take NEXPRO HP:**

- if you are allergic to amoxicillin, penicillin, clarithromycin, esomeprazole or any of the other ingredients of this medicine.
- if you have ever had an allergic reaction to any antibiotic. This can include a skin rash or swelling of the face or throat.
- If you are taking the following medications. Consult your doctor for advice on alternative medicines or ask if you are not sure:
- Ergotamine or dihydroergotamine tablets or use ergotamine inhalers (medicines used to treat

migraines).

- If you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, omeprazole).
- If you are taking a medicine containing nelfinavir (used to treat HIV infection).
- Combining these with NEXPRO HP may cause your blood vessels to narrow. This will lead to a decrease of blood supply to tissues.
- Cisapride (to treat stomach disorders), pimozide (to treat some mental illnesses), terfenadine or astemizole (to treat hay fever or allergy). Combining these medicines with NEXPRO HP can cause serious changes in your heart rhythm.
- Lovastatin or simvastatin (HMG-CoA reductase inhibitors, commonly known as statins, used to lower levels of cholesterol (a type of fat) in the blood).
- If your potassium levels are low (hypokalaemia)
- If you have severe liver disease with kidney disease
- If you have an irregular heart rhythm.

Do not take NEXPRO HP if any of the above apply. If you are not sure, talk to your doctor or pharmacist before taking NEXPRO HP.

**Warnings and Precautions**

Talk to your doctor, pharmacist or nurse before taking NEXPRO HP, if you:

- have glandular fever (fever, sore throat, swollen glands and extreme tiredness)
- have kidney problems, liver problems
- have, or are prone to, fungal infections (such as thrush)
- are not urinating regularly.
- are pregnant or breast feeding
- are due to have a specific blood test (Chromogranin A).

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking NEXPRO HP.

**Blood and urine tests**

If you are having:

- Urine tests (glucose) or blood tests for liver function
- Oestriol tests (used during pregnancy to check the baby is developing normally)

Tell your doctor or pharmacist that you are taking NEXPRO HP. This is because NEXPRO HP can affect the results of these tests.

**Other medicines and NEXPRO HP**

Tell your doctor or pharmacist, if you are taking, have recently taken or might take any other medicines.

You should not take NEXPRO HP if you are taking any of the following medicines:

- Cisapride (to treat stomach disorders)
- Pimozide (to treat mental illness)

- Terfenadine or astemizole (to treat hay fever or allergies)
- Ergotamine or dihydroergotamine (to treat migraines)
- Lovastatin or simvastatin (to treat high cholesterol)

Tell your doctor if you are taking any of the following medicines. Because of the possibility of reactions your doctor will decide if you can still take NEXPRO HP tablets:

- Colchicine (usually taken for gout). This may increase your risk of side effects and lead to potential toxicity.
- Digoxin (to treat heart failure). It may cause irregular heart beat and may also increase your risk of side effects.
- Quinidine or disopyramide (to treat abnormal heart rhythm). This may cause you to experience seriously irregular heart beat.
- Warfarin or acenocoumarol (to thin the blood). These medicines may change the rate at which your blood clots. This might result in toxic effects.
- Triazolam, alprazolam or midazolam (sedatives). These medicines may cause sleepiness and confusion.
- Rosuvastatin, atorvastatin (to treat high cholesterol). These medicines may lead to pain or weakness in muscles, or abnormal muscle breakdown. This can lead to kidney problems.
- Zidovudine (anti-viral agent). This may change the effectiveness of zidovudine.
- Rifabutin, rifampicin, rifapentin (to treat some infections). These medicines may change the effectiveness of NEXPRO HP.
- Efavirenz, nevirapine (HIV treatments). These medicines may change the effectiveness NEXPRO HP.

Taking the following medicines with NEXPRO HP may increase your risk of side effects. Tell your doctor if you are taking any of the following:

- Carbamazepine, valproate, phenobarbital or phenytoin (to treat epilepsy)
- Cilostazol (to treat poor circulation)
- Methylprednisolone (to treat inflammation)
- Sildenafil, tadalafil, vardenafil (to treat erection problems)
- Vinblastine (to treat cancer)
- Tolterodine (to treat urinary frequency)
- Omeprazole (to treat indigestion)
- Cyclosporin, tacrolimus, sirolimus (to help prevent rejection after a transplant)
- Theophylline (to treat asthma)
- Itraconazole or fluconazole (to treat fungal infections)
- Etavirine, ritonavir, atazanavir, saquinavir (anti-viral and anti-HIV medicines)
- Nateglinide, pioglitazone, repaglinide, rosiglitazone or insulin (to treat diabetes)
- Verapramil (to treat high blood pressure)
- Atazanavir (used to treat HIV infection).

- Clopidogrel (used to prevent blood clots).
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Erlotinib (used to treat cancer).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking NEXPRO HP.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking NEXPRO HP.
- Cilostazol (used to treat intermittent claudication – a pain in your legs when you walk which is caused by an insufficient blood supply).
- Cisapride (used for indigestion and heartburn).
- Digoxin (used for heart problems).
- Methotrexate (a chemotherapy medicine used in high doses to treat cancer) – if you are taking a high dose of methotrexate, your doctor may temporarily stop your NEXPRO HP treatment.
- Tacrolimus (organ transplantation).
- Rifampicin (used for treatment of tuberculosis).
- St. John's wort (Hypericum perforatum) (used to treat depression).
- If you are taking allopurinol (used for gout) with NEXPRO HP, it may be more likely that you will have an allergic skin reaction.
- If you are taking probenecid (used for gout), your doctor may decide to adjust your dose of NEXPRO HP.
- If you are taking medicines to help stop blood clots (such as warfarin), you may need extra blood tests.
- If you are taking other antibiotics (such as tetracycline) NEXPRO HP may be less effective.
- If you are taking methotrexate (used for the treatment of cancer and severe psoriasis) NEXPRO HP may cause an increase in side effects.

**Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

NEXPRO HP can have side effects and the symptoms (such as allergic reactions, dizziness and convulsions) may make you unfit to drive. Do not drive or operate machinery unless you are feeling well.

## 9.3.How to take NEXPRO HP

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Kidney problems**

If you have kidney problems the dose might be lower than the usual dose.

**If you take more NEXPRO HP than you should**

If you have taken too much of NEXPRO HP or if a child accidentally swallows some tablets, seek medical advice immediately. Take the medicine to show the doctor.

**If you forget to take NEXPRO HP**

- If you forget to take a dose, take it as soon as you remember.
- Do not take the next dose too soon, wait about 4 hours before taking the next dose.
- Do not take a double dose to make up for a forgotten dose.

**How long should you take NEXPRO HP for?**

- Keep taking NEXPRO HP for as long as your doctor has told you to, even if you feel better. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.
- Once you finish treatment, if you still feel unwell you should go back to see the doctor.

Thrush (a yeast infection of moist areas of the body which causes soreness, itching and white discharge) may develop if NEXPRO HP is used for a long time. If this occurs tell your doctor.

If you take NEXPRO HP for a long time, your doctor may perform additional tests to check your kidneys, liver and blood are working normally.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 9.4.Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking NEXPRO HP and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

The following are very rare (may affect up to 1 in 10,000 people)

- Allergic reactions, the signs may include: skin itching or rash, swelling of the face, lips, tongue, body or breathing difficulties. These can be serious and occasionally deaths have occurred
- Rash or pinpoint flat red round spots under the skin surface or bruising of the skin. This is due to inflammation of blood vessel walls due to an allergic reaction. It can be associated with joint pain (arthritis) and kidney problems
- A delayed allergic reaction can occur usually 7 to 12 days after having NEXPRO HP, some signs include: rashes, fever, joint pains and enlargement of the lymph nodes especially under the arms
- A skin reaction known as ‘erythema multiforme’ where you may develop: itchy reddish purple patches on the skin especially on the palms of the hands or soles of the feet, ‘hive-like’ raised swollen areas on the skin, tender areas on the surfaces of the mouth, eyes and genitals. You may have a fever and be very tired
- Other severe skin reactions can include: changes in skin colour, bumps under the skin, blistering, pustules, peeling, redness, pain, itching, scaling. These may be associated with fever, headaches and body aches
- Flu-like symptoms with a rash, fever, swollen glands, and abnormal blood test results (including increased white blood cells (eosinophilia) and liver enzymes) (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)).
- Fever, chills, a sore throat or other signs of an infection, or if you bruise easily. These may be signs of a problem with your blood cells

- The Jarisch-Herxheimer reaction which occurs during treatment with Amoxicillin for Lyme disease and causes fever, chills, headache, muscle pain and skin rash
- Inflammation of the large bowel (colon) with diarrhoea (sometimes containing blood), pain and fever
- Serious liver side effects may occur. They are mainly associated with people having treatment over a long period,males and the elderly.

You must tell your doctor urgently if you get:

- Severe diarrhoea with bleeding
- Blisters, redness or bruising of the skin
- Darker urine or paler stools
- Yellowing of the skin or the whites of the eyes (jaundice). See also anaemia below which might result in jaundice.
- Severe or prolonged diarrhoea, which may have blood or mucus in it (pseudomembranous colitis)
- Blistering of the skin, mouth, eyes or genitals (Stevens-Johnson syndrome)
- Henoch-Schonlein purpura (a rash which appears as purple spots on the skin)

These can happen when having the medicine or for up to several weeks after.

**If any of the above happens stop taking the medicine and see your doctor straight away.**

**Sometimes you may get less severe skin reactions such as:**

- A mildly itchy rash (round, pink-red patches), 'hive-like' swollen areas on forearms, legs, palms, hands or feet.

This is uncommon (may affect up to 1 in 100 people).

**If you have any of these talk to your doctor as Amoxicillin will need to be stopped.**

The other possible side effects are:

**Common** (may affect up to 1 in 10 people)

- Headache
- skin rash
- feeling sick (nausea)
- diarrhoea
- increased levels of urea in the blood (detected in laboratory tests)
- change in sense of taste, headache
- abdominal pain, diarrhoea, indigestion, feeling sick, vomiting, bloating, stomach pain, constipation, wind (flatulence).
- difficulty sleeping
- increased sweating
- Benign polyps in the stomach

**Other less common side effects**

- Presence of protein, blood or white blood cells in the urine, changes in liver or kidney function tests or blood tests, prothrombin time prolongation (increased blood clotting time)
- Leucopenia (reduction in the number of white blood cells, which makes infections more likely), Anaemia (decrease in red blood cells, which can make the skin pale and cause weakness and breathlessness), eosinophilia (blood disorder), thrombocythaemia (increase in blood platelets, which increases the risk of bleeding or blood clots)
- Tremor (shaking)
- Tinnitus (ringing in the ears) or hearing loss, vertigo (spinning sensation)
- Constipation, dry mouth, belching, flatulence (wind), bleeding from stomach and intestines
- Back, joint or muscle pain
- If you suffer from myasthenia gravis (a condition in which the muscles become weak and tire easily) clarithromycin may worsen these symptoms
- Gastroenteritis (inflammation of the stomach and intestines), oral thrush, vaginal bacterial or fungal infection
- Allergic reactions ranging from urticaria (nettle rash), mild skin eruptions and angioedema (swelling of the hands and face) to anaphylaxis (severe allergic reaction)
- Liver dysfunction or hepatitis (inflammation of the liver), cholestasis (obstruction of bile), jaundice (yellowing of the skin and whites of the eyes), hyperbilirubinaemia (increase of bilirubin in blood), Liver failure
- sleepiness or difficulty in sleeping, nervousness
- Anorexia (loss of appetite)
- Widening of blood vessels
- Shortness of breath or other problems with breathing including asthma
- Feeling of weakness or discomfort, lethargy, fatigue, thirst, water retention in face (oedema), general feeling of being unwell, chest pain or any other pain
- Loss of taste or smell or inability to smell properly
- Discolouration of the tongue or teeth
- Inflammation of the mouth or tongue
- Heart rhythm disturbances or palpitations
- Hypoglycaemia (low blood sugar)
- Life-threatening irregular heart beat
- Tingling or numbness of limbs, convulsions (fits)
- Pancreatitis (inflammation of the pancreas), Pseudomembranous colitis (infection of the bowel)
- Kidney failure, interstitial nephritis (inflammation of the kidneys)
- Toxic epidermal necrolysis (severe peeling and blistering of the skin)
- Bad dreams, anxiety, confusion, depersonalisation (out of body feeling), disorientation (not knowing where you are), hallucinations, psychosis (mental illness)
- Acne

• Deafness

**Uncommon** (may affect up to 1 in 100 people)

• Swelling of the feet and ankles

• Disturbed sleep (insomnia).

• Dizziness, feeling sleepy

• Spinning feeling (vertigo).

• Changes in blood tests that check how the liver is working.

• Skin rash, lumpy rash (hives) and itchy skin.

• Fracture of the hip, wrist or spine (if NEXPRO HP is used in high doses and over long duration).

**Rare (may affect up to 1 in 1,000 people)**

• Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.

• Feeling agitated, confused or depressed.

• Taste changes.

• Eyesight problems such as blurred vision.

• Suddenly feeling wheezy or short of breath (bronchospasm).

• An inflammation of the inside of the mouth.

• An infection called "thrush" which can affect the gut and is caused by a fungus.

• Hair loss (alopecia).

• Skin rash on exposure to sunshine.

• Joint pains (arthralgia) or muscle pains (myalgia).

• Generally feeling unwell and lacking energy.

• Increased sweating.

**Very rare** (may affect up to 1 in 10,000 people)

• Thrush (a yeast infection of the vagina, mouth or skin folds), you can get treatment for thrush from your doctor or pharmacist

• Kidney problems

• Fits (convulsions), seen in patients on high doses or with kidney problems

• Dizziness

• Hyperactivity

• Crystals in the urine, which may be seen as cloudy urine, or difficulty or discomfort in passing urine. Make sure you drink plenty of fluids to reduce the chance of these symptoms

• Teeth may appear stained, usually returning to normal with brushing (this has been reported in children)

• The tongue may change to yellow, brown or black and it may have a hairy appearance

• An excessive breakdown of red blood cells causing a type of anaemia. Signs include: tiredness, headache, shortness of breath, dizziness, looking pale and yellowing of the skin and the whites of the eyes

- The blood may take longer to clot than it normally would. You may notice this if you have a nosebleed or cut yourself.

**Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting

## 9.5. How to store NEXPRO HP

Store at a temperature not exceeding 30°C, Protected from light and moisture.

## 9.6. Contents of the pack and other information

NEXPRO HP Kit is available as strip of 6 tablets. It is a combi pack of Clarithromycin 500 mg Film coated tablet (2), Amoxicillin 750 mg Film coated tablet (2) and Esomeprazole 40 mg Enteric coated tablet (2).

The excipients used are:

**Clarithromycin**

Microcrystalline Cellulose, Pregelatinised Starch, Polyvinyl Pyrrolidone, Ac-di-sol, Talcum, Starch, Colloidal Silicon Dioxide, Stearic acid, Magnesium Stearate, HPMC, Isopropyl Alcohol, Methylene Chloride, PEG 6000 and Titanium Dioxide

**Amoxicillin**

Starch, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, PEG 6000, Titanium Dioxide, Methylene Chloride, HPMC and Sunset Yellow

**Esomeprazole**

Mannitol, Sodium Lauryl Sulfate, Polyvinyl Pyrrolidone, Sodium Carbonate, Sodium Stearyl Fumarate, Microcrystalline Cellulose, Crospovidone, Talcum, HPMC, Methacrylic acid Ethylacrylic acid copolymer dispersion, Triethyl citrate, Titanium Dioxide, Red Oxide of Iron, PEG 6000

## 10. Details of manufacturer

Malik Lifesciences Pvt. Ltd.

Plot No. 16, Vardhman Industrial Estate,

Vill-Bahadarpur Saini, N.H.58, Haridwar – 247667 (Uttarakhand).

## 11. Details of permission or licence number with date

Mfg. Lic. No.: 48/UA/SC/P-2013 issued on 01.04.2015

## 12. Date of revision

JUN/2020

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/NEXPRO HP KIT 500,40,750mg/JUN-20/03/PI**