SUMMARY OF PRODUCT CHARACTERISTICS

G- KIT (Amoxicillin Tablets BP 1000 mg, Clarithromycin Tablets BP 500 mg & Esomeprazole Tablets 20 mg)

Section 1 Product Description

Name of the medicinal product

G- KIT (Amoxicillin Tablets BP 1000 mg, Clarithromycin Tablets BP 500 mg & Esomeprazole Tablets 20 mg)

Section 2 Qualitative and Quantitative Composition

Label Claim:

Each Kit Contains:

A) Amoxicillin Tablets BP 1000 mg (2 Tablets)

Each film coated tablet contains:

Amoxicillin trihydrate BP

Eq. to Amoxicillin…….1000 mg

Excipients……Q.S.

Colour: Titanium Dioxide

B) Clarithromycin Tablets BP 500 mg (2 Tablets)

Each film coated tablet contains:

Clarithromycin BP……500 mg

Excipients…….Q.S.

Colour: Quinoline Yellow

C) Esomeprazole Tablets 20 mg (2 Tablets)

Each Enteric coated tablets contains:

Esomeprazole Magnesium Trihydrate BP

Eq. to Esomeprazole…….20 mg

Excipients……....Q.S.

Colour: Sunset Yellow

Section 3. Pharmaceutical Form

Two Film Coated and Enteric coated Tablets

Visual Description of the product

Amoxicillin Tablets BP 1000 mg

White to off white colored oval shaped film coated Tablets.

Clarithromycin Tablets BP 500 mg

Yellow Colored, Caplet Shaped, Film coated Tablets Having Break line on one side and plain on other side.

Esomeprazole Tablets 20 mg

Orange Colored, round shape, biconvex, enteric-coated tablet.

Section 4. Clinical Particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The recommended dosage regimen of G- KIT is Esomeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily for 7 days. Consult each individual Product Information documents for further advice on methods of administration.

Use in children: G- KIT should not be used in children since no data is available.

Geriatrics: Although this regimen has not been specifically studied in the elderly, dosage adjustment is not needed during therapy with the individual components. It is therefore unlikely to require dosage adjustment with G- KIT.

Renal Insufficiency: Patients with impaired kidney function require a reduced dose of both amoxicillin, and clarithromycin. In renal impairment the excretion of amoxicillin will be delayed and depending on the degree of impairment, it may be necessary to reduce the total daily dosage. In patients receiving peritoneal dialysis, the maximum recommended dose is 500 mg/day. Amoxicillin may be removed from the circulation by hemodialysis.

Section 4.3 Contraindications

- Hypersensitivity to esomeprazole, substituted benzimidazoles, β-lactam antibiotics (e.g. penicillins, cephalosporin), clarithromycin, or any other constituents of the formulations.
- History of an allergic reaction to penicillins or any macrolide antibiotic drugs
- Clarithromycin is contraindicated as concurrent therapy with astemizole, terfenadine, cisapride and pimozide as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.
- Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.
- Concomitant administration of clarithromycin with lovastatin or simvastatin is also contraindicated.
- Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes.
- Esomeprazole like other proton pump inhibitors should not be administered with Atazanavir.
- Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking Cilostazol.

Section 4.4 Special warnings and precautions for use

When prescribing esomeprazole for eradication of Helicobacter pylori possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalized patients, possibly also Clostridium difficile. Adequate fluid intake and urinary output must be maintained in patients receiving high doses of amoxicillin. Abnormal prolongation of

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

Undiagnosed Malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with G- KIT may alleviate symptoms and delay diagnosis.

Anaphylaxis

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

Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

Myasthenia gravis

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

Pseudo membranous colitis

Antibiotic associated pseudo membranous colitis has been reported with many antibiotics including amoxicillin and macrolides. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe

cases appropriate therapy with a suitable oral antibiotic agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

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

Super infection

The possibility of super infections with mycotic or bacterial pathogens should be kept in mind during therapy. If super infections occur (usually involving Agrobacteria, Pseudomonas or Candida), the amoxicillin and clarithromycin components should is discontinued and/or appropriate therapy instituted.

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens.

The clinical impact of this resistance of H. pylori eradication has not been comprehensively studied.

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

Lymphatic Leukemia

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

Colchicine

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

QT Prolongation and Torsades de pointes

1Due to the risk for QT prolongation clarithromycin should be used with caution in patients with a medical condition associated with an increased tendency toward QT prolongation and torsades de pointes.

Triazolobenzodiazepines

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

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 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-Schönlein 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

Oral Hypoglycaemic Agents/Insulin Clarithromycin:

The concomitant use of clarithromycin and oral hypoglycaemic agents and/or insulin can result in significant Hypoglycemia. With certain hypoglycaemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause Hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral Anticoagulants Clarithromycin:

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.

HMG-CoA Reductase Inhibitors Clarithromycin:

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated and treatment with these agents should be discontinued during clarithromycin treatment. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

Special Patient Populations CYP2C19 enzyme Esomeprazole

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

Esomeprazole

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

Hepatic Insufficiency

Esomeprazole

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired; however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing

Clarithromycin

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

Impaired Renal Function

Esomeprazole

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Amoxycillin

Excretion of amoxycillin is delayed in patients with renal impairment, and depending on the degree of impairment, it may be necessary to reduce the total daily dosage.

Clarithromycin

The plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-hydroxy metabolite are higher, and the AUC larger, in patients with renal impairment. Plasma levels and elimination half-life start increasing at creatinine clearance values of less than 30 mL/minute. In the presence of significant renal impairment, with or without co-existing hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate. Caution is advised in patients with severe renal insufficiency.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Section 4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 Effects

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

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolizing enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Esomeprazole has been shown to interact with diazepam, phenytoin, warfarin, citalopram, clomipramine, imipramine and Atazanavir. Further information is provided below. Details of other drugs metabolised via the cytochrome P450 system which have been shown not to be affected by concomitant esomeprazole treatment may be obtained from the this Product Information.

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

Other drugs that affect esomeprazole, amoxicillin or clarithromycin

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Fluconazole

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

HIV Protease Inhibitors

Ritonavir. A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every twelve hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased by 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients.

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with G- KIT may result in increased and prolonged blood levels of amoxicillin.

Others

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required. CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP 3A4 other than clarithromycin (eg. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

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

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis. Drugs known to induce CYP2C19 or CYP3A4 or

both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Fluoxetine

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

Efavirenz, Nevirapine, rifabutin and rifampicin

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, Nevirapine, rifampicin and rifabutin may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OHclarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

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

Effects of esomeprazole, amoxycillin or clarithromycin on other drugs

Allopurinol

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

Carbamazepine

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

Cisapride, Pimozide, Terfenadine and Astemizole

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

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 Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Citalopram, clomipramine and imipramine

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

Diazepam

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

Methotrexate

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

HIV Protease Inhibitors

Atazanavir and nelfinavir. Concomitant administration with esomeprazole and atazanavir is contraindicated. Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have

been reported when given with omeprazole. Due to the similar Pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

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

Ritonavir. Ritonavir produces a 77% increase in clarithromycin AUC but a 99.8% decrease in 14- hydroxy-clarithromycin AUC; no dosage reduction of clarithromycin is recommended except in decreased renal function. Conversely, clarithromycin increases ritonavir AUC by 12%; no dosage adjustment of ritonavir is recommended.

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

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

Zidovudine. Simultaneous oral administration of clarithromycin and zidovudine in HIV infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can largely be avoided by staggering the doses of clarithromycin

and zidovudine by at least two hours. This interaction does not appear to occur in paediatric HIV infected patients taking clarithromycin suspensions with zidovudine or didanosine.

Verapamil

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

HMG-CoA reductase inhibitors

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

Oral contraceptives

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

Phenytoin

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

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

Valproate

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

Antiarrhythmics (quinidine or disopyramide)

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

Repaglinide

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

Tetracyclines

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

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

Oral anticoagulants

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

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

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

Ergotamine / dihydroergotamine

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

Terfenadine

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, and ventricular fibrillation and torsades de pointes. Concomitant use with this medication is therefore contraindicated.

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.

Sildenafil, tadalafil and vardenafil

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

Tolterodine

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

Digoxin

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (Pgp) by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Medicinal products with pH dependent absorption

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

CYP3A-based interactions

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

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

There have been reports of clarithromycin interactions with cyclosporin, ergotamine and tacrolimus. Cyclosporin, ergotamine and tacrolimus are metabolised by CYP3A. As with other macrolide antibiotics, the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (eg alprazolam, cilostazol, oral anticoagulants such as warfarin, ergot alkaloids, methylprednisolone, quinidine, triazolam, valproate,

vinblastine, midazolam, disopyramide, phenytoin, digoxin, tacrolimus, cyclosporin, rifabutin and sildenafil) may be associated with elevations in serum levels of these drugs.

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

Erythromycin has been reported to decrease clearance of triazolam and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment.

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

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

Food

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

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

Section 4.6 Fertility, pregnancy and lactation

Pregnancy

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

For further information regarding the use of G- KIT in pregnancy, refer to the full Product Information for the appropriate component.

Lactation

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

For further information regarding the use of G- KIT in lactation, refer to the full Product Information for the appropriate component.

Fertility

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

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

There is no data available on the effect of clarithromycin on fertility in humans. In rats, the limited data available do not indicate any effects on fertility

Section 4.7 Effects on ability to drive and use machines

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

Section 4.8 Undesirable effects

Esomeprazole

System Organ Class	**Frequency**	**Event**
Blood and lymphatic system disorders	Rare	leukopenia, thrombocytopenia
Very rare	agranulocytosis, pancytopenia	
Immune system disorders	Rare	hypersensitivity reactions e.g. angioedema, anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	peripheral oedema
Rare	hyponatremia	
Very rare	hypomagnesaemia	
Psychiatric disorders	Uncommon	insomnia
Rare	agitation, confusion, depression	
Very rare	aggression, hallucination	

Nervous system disorders	Common	headache
Uncommon	dizziness, paresthesia, somnolence	
Rare	taste disturbance	
Eye disorders	Rare	blurred vision, visual accommodation disturbances
Ear and labyrinth disorders	Uncommon	vertigo

Clarithromycin

Body System	**Adverse Reaction**
Skin and Skin Structure	Stevens-Johnson Syndrome, urticaria, rash, pruritus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Henoch-Schönlein purpura
Central Nervous System	Anxiety, insomnia, hallucinations, confusion, psychosis, vertigo, dizziness, dream abnormality, tinnitus, disorientation, depersonalization, nervousness, hyperkinesia, depression. There have been rare reports of convulsions.
Hematopoietic & Lymphatic system	decreased white blood cell counts, decreased platelet counts, thrombocytopenia, leukopenia, agranulocytosis
Metabolic & Nutritional	increased serum creatinine, increased gamma glutaryl, transferase (GGT), hypoglycaemia1
Special Senses	hearing disturbances, taste perversion, smell perversion, ageusia, anosmia otitis media
Digestive System	dry mouth, tongue discoloration, glossitis, moniliasis oral, stomatitis, diarrhea, nausea, vomiting, liver abnormalities, tooth discoloration, dyspepsia, enteritis. There have been rare reports of pancreatitis.
Respiratory System	dyspnea
Urogenital System	Dysuria, renal failure, isolated cases of increased serum creatinine have been reported but an association has not been established. There have been reports of interstitial nephritis coincident with clarithromycin use.
Cardiac System2	torsade de pointes, electrocardiogram QT prolonged, ventricular tachycardia,
Hepatobiliary System3	hepatic failure, hepatitis, hepatitis cholestatic, jaundice cholestatic, jaundice hepatocellular, hepatic function abnormal
Musculoskeletal and Connective Tissue Disorders4	myalgia, rhabdomyolysis, myopathy

Infections and Infestations	pseudomembranous colitis, erysipelas, erythrasma
Vascular Disorders	hemorrhage
Investigations	International Normalized Ratio (INR) increased, prothrombin time prolonged, urine colour abnormal

Amoxicillin

Hypersensitivity reactions: Erythematous maculopapular rash, pruritus and urticaria have been reported occasionally. Rarely, skin reactions such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous, exfoliative dermatitis and acute generalized exanthematous pustulosis (AGEP) have been reported. As with other antibiotics, severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness, hypersensitivity Vasculitis and interstitial nephritis have been reported rarely. Whenever such reactions occur, amoxycillin should be discontinued. (Note: Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.) Anaphylaxis is the most serious reaction experienced

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

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

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

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via National Regulatory Agenys

Section 4.9 Overdose

Esomeprazole

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Clarithromycin

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

Amoxicillin

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water/electrolyte imbalance should be treated symptomatically.

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

Section 5. Pharmacological Properties

5.1 Pharmacodynamic properties

Esomeprazole

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphonamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pent gastrin stimulation is decreased 90% when measured 6 – 7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The 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%.

Therapeutic effects of acid inhibition

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

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

Clarithromycin

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally twofold lower than the MICs of erythromycin. The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-

fold higher than the MICs of the parent compound, except for H. influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Amoxicillin

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

5.2 Pharmacokinetic properties

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. Esomeprazole should be taken at least 1 hour before meals. AUC was decreased by 33% to 53% after food intake compared to fasting, based on a single 40-mg dose (delayed-release capsules).

Distribution and Protein Binding:

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.

Metabolism:

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. 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.

Elimination:

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a 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. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Clarithromycin

Absorption: Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg tablets is approximately 50%. Food intake half an hour before tablet dosing increased both the rate and extent of clarithromycin absorption. In a study on the 250 mg tablets, the mean Cmax and area under the plasma concentration curve (AUC) values were 0.72 ± 0.27 μg/mL and 4.3 ± 1.5 μg.h/mL (fasting) and 0.84 ± 0.38 μg/mL and 4.7 ± 1.7 μg.h/mL (nonfasting), respectively. The consequences for clinical efficacy of the increase in bioavailability caused by food are not known.

In studies of fasting healthy adults, peak serum concentrations were attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in 2 to 3 days and were approximately 1 μg/mL with a 250 mg dose administered every 12 hours and 2-3 μg/mL with a 500 mg dose administered every 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 12 hours. The non-linearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 12 hours but is quite marked at higher doses. With a 250 mg every 12 hours dosing, the principal metabolite, 14-hydroxyclarithromycin attains a peak steady-state concentration of about 0.6 μg/mL and has an elimination half-life of 5 to 6 hours. With a dose of 500 mg every 12 hours, the peak steady-state concentrations of 14-hydroxy-clarithromycin are slightly higher (up to 1 μg/mL) and its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Distribution and Plasma Protein Binding:

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

Metabolism: Studies demonstrate that clarithromycin undergoes cytochrome-P450 dependent Ndemethylation and 14-(R)-hydroxylation in the presence of human liver microsomes.

Elimination:

Approximately 20% of a 250 mg oral dose given every 12 hours is excreted in the urine as unchanged clarithromycin. After a dose of 500 mg every 12 hours, urinary excretion of unchanged parent drug is approximately 30%. The renal clearance of clarithromycin is however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is14-hydroxy-clarithromycin which accounts for an additional 10-15% of either a 250 mg or 500 mg dose administered every 12 hours.

Amoxicillin

Amoxicillin is stable in the presence of gastric acid and is rapidly and well absorbed after oral administration, even in the presence of food. Amoxicillin diffuses rapidly into most body tissues and fluids, with the exception of brain and spinal fluid except when meninges are inflamed. Amoxicillin has been shown to diffuse into sputum and saliva and is excreted mainly via the urine where it exists in a high concentration. The amount to be found in the bile is variable, depending on normal biliary secretory function.

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

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

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

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

5.3 Preclinical safety data

Esomeprazole

Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. 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.

Clarithromycin

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported In vitro and in vivo studies showed that clarithromycin did not have genotoxic potential.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (IV) and x10 the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryo toxicity or teratogenicity was generally noted in rat studies. However, cardiovascular malformations were observed in two studies in rats treated with doses of 150 mg/kg/d. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%). Clarithromycin has been found in the milk of lactating animals.

Amoxicillin

Not Known

Section 6. PHARMACEUTICAL PARTICULARS

Section 6.1 List of excipients

Amoxicillin Tablets BP 1000 mg

Lactose BP/USP

M.C.C.P. Powder BP/USP

P.V.P.K-30 BP/USP

Iso Propyl Alcohol BP/USP

Magnesium Stearate BP/USP

Aerosil BP/USP

Kyron T-314 spcl BP/USP

Talcum BP/USP

Sodium starch Glycolate BP/USP

Cross Carmelose Sodium USP

Film Coat Titanium Dioxide IHS

Iso Propyl Alcohol BP/USP

Methylene Dichloride BP/USP

Clarithromycin Tablets BP 500 mg

Starch BP/USP

M.C.C powder BP/USP

Cross Carmelose Sodium USP

P.V.P.K-30 BP/USP

Sodium Benzoate BP/USP

Magnesium Stearate BP/USP

Cross Povidone XL-10 BP/USP

Sodium starch Glycolate BP/USP

Aerosil BP/USP

Talcum BP/USP

Kyron T-314 IHS

Film Coat quinolone yellow IHS

Methylene Dichloride BP/USP

Iso Propyl Alcohol BP/USP

Esomeprazole Tablets 20 mg

M.C.C.P.1 (AVICEL-102) IHS

Magnesium Oxide IHS

Mannitol BP

Magnesium Stearate BP/USP

Talcum BP/USP

Sodium starch Glycolate BP/USP

Aerosil BP/USP

Cross Carmelose Sodium BP/USP

Film Coat Titanium Dioxide BP/USP

Iso Propyl Alcohol BP/USP

Methylene Dichloride BP/USP

Colour coat EC4S Sunset yellow IHS

Section 6.2 Incompatibilities

Not applicable

Section 6.3 Shelf life

36 Months

Section 6.4 Special precautions for storage

Store below 30°C. Keep this medicine out of reach of children

Section 6.5 Nature and contents of container

1 Kit of 6 tablets consisting of
2 Amoxicillin Tablets BP 1000 mg
2 Clarithromycin Tablets BP 500 mg
2 Esomeprazole Tablets 20 mg are packed in Aluminium Strips pack.

Such 7 Kits are packed in a printed outer carton along with a pack insert.

Section 6.6 Special precautions for disposal and other handling:

No special handling requirements. Any unused product or waste material should be disposed of in accordance with local requirements

Section 7. Marketing Authorization Holder

Marketing Authorisation Holder:

PROMED PHARMACY LTD

Colchester Park,

P.O BOX 17843 – 00500

Nairobi -Kenya.

Section 8. Marketing Authorisation Number(s)

Section 9. Date of First Authorisation/Renewal of the Authorisation

Section 10. Date of Revision of the Text