Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ESOGLAX HP Kit

2. Qualitative and quantitative composition

Amoxicillin Tablets BP:
Each film coated tablet contains, Amoxicillin Trihydrate BP Eq. to Amoxicillin 1000 mg.

Clarithromycin Tablets USP:
Each film coated tablet contains, Clarithromycin USP 500 mg

Esomeprazole Tablets:
Each enteric coated tablet contains: Esomeprazole Magnesium Trihydrate BP Eq. to Esomeprazole 20 mg
Excipient with known effect
Mannitol

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Amoxicillin Tablets BP
Film-coated tablet, White, elongated, biconvex, scored on one side, plain on other side, film coated tablets.

Clarithromycin Tablets USP
Film-coated tablet, White, elongated biconvex, scored on one side, plain on other side, film coated tablets.

Esomeprazole Tablets
Enteric-coated tablet, White, Round, biconvex, plain on both sides, enteric coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

ESOGLAX HP Kit is indicated in the eradication of H. pylori in active chronic gastritis, duodenal and gastric ulcers.

4.2 Posology and method of administration

ESOGLAX HP Kit contains 7 kits to be taken in 7 days.
Each one-day kit contains:
Two Amoxicillin 1000 mg film coated Tablets, Two Clarithromycin 500 mg film coated Tablets and Two Esomeprazole 40 mg Gastro-resistant Tablets.

One tablet of amoxicillin 1000mg, one tablet of clarithromycin 500mg and one tablet of esomeprazole 40 mg should be taken every morning and a repeat of the same every evening for the duration of therapy.
The recommended therapy is for seven days and may be extended as per the Physicians advice.
Esomeprazole gastro-resistant tablets, clarithromycin and amoxicillin tablets should not be crushed or chewed, and should be swallowed whole with a glass of water.

Special Populations
Paediatric Use
ESOGLAX HP Kit should not be used in paediatric patients since no data is available.

Method of administration
For oral use. Esomeprazole gastro-resistant tablets, Clarithromycin tablets and amoxicillin film-coated tablets should not be crushed or chewed, and should be swallowed whole.

4.3 Contraindications
A history of allergic reaction to any of the penicillins and infections caused by penicillinase producing organism are contraindicated.
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.
Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a p-glycoprotein inhibitor or a strong CYP3A4 inhibitor.
Esomeprazole like other proton pump inhibitors should not be administered with Atazanavir Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking Cilostazol.
Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed in section 6.1. Esomeprazole should not be used concomitantly with nelfinavir and atazanavir.

4.4 Special warnings and precautions for use
Before initiating therapy with ESOGLAX HP Kit, carefully inquire from the patient concerning hypersensitivity to penicillinS cephalosporin and other allergens. Serious and occasionally fatal hypersensitivity reactions (anaphylactic) have been reported in patients on penicillin therapy.

When prescribing Esomeprazole for eradication of Helicobacter pylori, possible drug interactions for all components in the triple therapy should be considered. Caution should be taken when using fluroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III
antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction,bradycardia)
Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken.

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

Clarithromycin
Clarithromycin should not be used in pregnant women without careful evaluation of the risks against the benefits, especially during the first trimester of pregnancy.
Clarithromycin is primarily metabolised in the liver. Therefore, caution should be exercised in administering his antibiotic in patients with impaired liver function.
Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, 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. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the

administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. 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 (see section 4.5). 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 with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

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.
Convulsions
Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors
Renal impairment
In patients with renal impairment, the dose should be adjusted according to the degree of impairment. PYLOBACT NEO 2 is not recommended for use in patients requiring any kind of dose adjustment.
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.
Crystalluria In patients with reduced urine output, crystalluria has been reported 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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

Esomeprazole 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.

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.

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.

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.

Clarithromycin

Cisapride, pimozide, astemizole and terfenadine

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

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 (see section 4.3, Contraindications).

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.

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

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

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.
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 (see section 4.4 Warnings and Precautions)

Amoxicillin:
1. Allopurinol may increase possibilities of hypersensitivity reactions.
2. Chloramphenicol, tetracyclines, Sulphonamides and macrolide antibiotics may interfere with bactericidal effects of penicillins.
3. Oral contraceptives may be less effective and increase break through bleeding may occur.
4. Probenecid may decrease renal tubular secretion of Amoxicillin resulting in its increased blood levels and or Amoxicillin toxicity.

4.6 Fertility, Pregnancy and Lactation

Amoxicillin
Use in pregnancy:
Animal studies with Amoxicillin have shown no teratogenic effects. The product has been in extensive clinical use since 1972 and its suitability in human pregnancy has been well documented in clinical studies. When antibiotic therapy is required during pregnancy, Amoxicillin may be considered appropriate when the potential benefits outweigh the potential risks associated with treatment.
Use in lactation:
Amoxicillin may be given during lactation. With the exception of the risk of sensitization associated with the excretion of trace quantities of amoxicillin in breast milk, there are no known detrimental effects for the breast-fed infant.

Esomeprazole
Pregnancy
Clinical data on exposed pregnancies with Esomeprazole are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. 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.

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.

Clarithromycin

Fertility:

Fertility studies have not shown any evidence of harmful effects in rats

Pregnancy

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

Breast-feeding

The safety of clarithromycin for use during breastfeeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been established that an exclusively breastfed infant would receive about 1.7% of the maternal weight adjusted dose of clarithromycin.

4.7 Effects on ability to drive and use machines

Esomeprazole

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

Clarithromycin

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

Amoxicillin

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Esomeprazole

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 (see section 4.4); 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
	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 preexisting liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity

	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders		Uncommon Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

System Organ Class	Very common (≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Not Known* (cannot be estimated from the available data)
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2],infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache,	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsade de pointes, ventricular tachycardia ventricular fibrillation
Vascular disorders		Vasodilation[1]		Hemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	

Gastrointestinal disorders		Diarrhoea[9], vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis, gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Severe cutaneous adverse reactions (SCAR) e.g. acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2]**, myopathy
Renal and urinary disorders			Blood creatinine increased[1],	Renal failure,

			blood urea increased[1]	nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis [1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine color abnormal

Amoxicillin
As with other penicillin, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillin and in those with a history of allergy, asthma, hay fever or uetica. The following adverse reactions have been reported as associated with the use of penicillin.

Gastrointestinal: Glossitis, stomatits, nausea, vomiting, diarrhea, entero- colis and pseudomembranous colitis. These reactions are usually associated with oral dosage forms of the drug.
Hypersensitivity: Occurrence of an erythematous, midly pruritic; maculopapular skin rash has been reported.

4.9 Overdose

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.

Clarithromycin
Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. 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 the prompt elimination of 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 should be treated symptomatically with attention to the water/electrolyte balance. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.

Amoxicillin may be removed from the circulation by haemodialysis.

5. Pharmacological properties
5.1 Pharmacodynamic properties

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 week 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.

Clarithromycin
Pharmacotherapeutic group: Antibacterial for systemic use, macrolides

ATC Code: J01FA09
Mechanism of action:
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
Clarithromycin demonstrates excellent *in vitro* activity against standard strains of clinical isolates. 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 two-fold lower than the MICs of erythromycin.
In vitro studies also indicate very strong activity of clarithromycin on Legionella pneumophila and Mycoplasma pneumoniae. Clarithromycin has a bactericidal effect on Helicobacter pylori, the effect being stronger in an inert environment than in an acidic environment.

Amoxicillin
Pharmacotherapeutic group: Penicillins with extended spectrum; ATC Code J01CA04
Mechanisms of Action/Effect
Amoxicillin is similar to penicillin in its bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.
Amoxicillin is bactericidal. Like all penicillins it acts by interfering with the synthesis of the cell wall of the bacterium.
Amoxicillin is inactivated by penicillinase. Penicillinase-producing strains of Staphylococcus aureus and Gram-negative organisms (e.g. Escherichia coli, Proteus, Klebsiella) are resistant.

Complete cross-resistance occurs with ampicillin and amoxicillin.

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. 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 twice daily 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.

Older people

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 drug concentration (tmax) in 12- to 18-year-olds was similar to that in adults for both Esomeprazole doses.

Clarithromycin

Absorption:

The pharmacokinetic properties of clarithromycin administered orally have been evaluated in a number of studies conducted on many animal species and in adult humans. These studies have shown that clarithromycin is well and rapidly absorbed from the gastrointestinal tract, and its bioavailability is about 50%. There was no accumulation of the drug or it was small. The consumption of food immediately before the dose administration increases the bioavailability of clarithromycin by an average of 25%, which is of little clinical relevance when used at the recommended dosage. Clarithromycin can therefore be administered with food or on an empty stomach.

Distribution, biotransformation, elimination:

In vitro

In vitro, clarithromycin was shown to bind to human plasma proteins at approximately 70% when its concentration is between 0.45 and 4.5 μ g/ml. A reduction in the percentage of antibiotic associated with proteins to 41% was observed when its concentration was 45.0 μ g/ml, indicating that all binding sites of the drug are likely to be saturated. However, this occurs only when the concentration of antibiotic is significantly higher than the therapeutic concentration.

In vivo

The results of animal studies showed that the concentration of clarithromycin in all tissues, with the exception of the central nervous system, was several times higher than in the blood concentration. The highest concentrations were usually found in the liver and lungs, where

the ratio of drug concentrations in tissue to plasma concentrations ranged from 10 to 20.

Healthy persons

After an oral dose of 250 mg twice daily, steady-state is achieved after 2-3 days. At steady-state the mean maximum plasma clarithromycin concentration is approximately 1 µ g/ml, and the concentration of 14-OH-clarithromycin 0.6 µ g/ml. The half-lives of the parent compound and the active metabolite are 3-4 hours and 5-6 hours, respectively. Oral administration of clarithromycin 500 mg twice daily resulted in the maximum steady-state drug and active metabolite (C_{max}) concentrations achieved after the fifth dose. After the fifth and seventh doses, the mean clarithromycin Cmax values were 2.7 and 2.9 µ g / ml, respectively, and 14-OH-clarithromycin 0.88 and 0.83 µ g/ml. After administration of 500 mg, the half-life of clarithromycin was 4.5-4.8 hours, and 14-hydroxymetabolite was 6.9-8.7 hours. It has been shown that after reaching steady state, increasing the dose does not increase the concentration of 14-OH-clarithromycin, while the half-life of clarithromycin and its metabolite is prolonged. These non-linear changes in the pharmacokinetic parameters of clarithromycin in combination with the formation of 14-hydroxylation and N-demethylation products limitation indicate that the non-linear course of the drug metabolism is more pronounced at high doses.

Clarithromycin is metabolised in the liver. After a single oral administration of 250 mg or 1.2 g of clarithromycin in urine, 37.9% or 46% of the administered dose is excreted, respectively, and 40.2% or 29.1% in faeces.

Patients

Clarithromycin and its metabolite, 14-OH-clarithromycin, penetrate rapidly into tissues and body fluids. Limited data from a small number of patients indicate that clarithromycin does not reach significant concentrations in the cerebrospinal fluid after oral administration. (In patients with normal blood-cerebrospinal fluid barrier, the clarithromycin concentration in the cerebrospinal fluid is only 1 to 2% of the concentration found in the serum). The concentration in tissues is usually several times higher than in serum concentration. Examples of concentrations in tissues and serum are given below**.**

CONCENTRATION (after 250 mg every 12 h)		
Type of tissue	Tissue (µ g/g)	Serum
		(µ g/ml)
Palatine tonsil	1,6	0,8
Lung	8,8	1,7

Liver failure

In a trial comparing healthy adults to a group of patients with liver failure, 250 mg of clarithromycin twice daily for two days and a single dose of 250 mg on the third day were administered. There were no significant differences between plasma clarithromycin at steady state and total drug clearance in both groups. In contrast, steady state

concentrations of 14-hydroxymetabolite were significantly lower in the group of patients with liver failure. The reduction in the formation of 14-OH-clarithromycin in the liver was partially compensated for by increasing the renal clearance, thanks to which the steady state concentrations of the drug were comparable in patients with liver failure and in healthy subjects. This study shows that there is no need to change the dosage in patients with moderate or severe liver failure, but normal renal function.

Renal failure

The pharmacokinetic parameters of clarithromycin after multiple oral doses of 500 mg to patients with normal renal function and renal failure were compared. In patients with renal failure there was an increase in plasma concentration, half-life, C_{max} and C_{min}, and AUC of clarithromycin and its 14-hydroxymethabolite. The K_{-elim} value and urinary excretion were reduced. The difference between these parameters correlated with the degree of renal failure, i.e. the more severe renal failure, the more significant the difference (see section 4.2).

Elderly patients

A study was conducted to compare the safety and pharmacokinetic profile of clarithromycin after repeated oral administration of doses of 500 mg to healthy elderly men and women and healthy young men. In the elderly group, plasma concentrations of the drug and its metabolite were higher, and the excretion was slower than in the group of young people. There were, however, no differences between the two groups when renal clearance was correlated with creatinine clearance. The research shows that all changes in the metabolism of clarithromycin in the body depend on kidney function, not on age.

Infections caused by Mycobacterium avium

The concentration of clarithromycin and its metabolite at steady-state in adult patients infected with human immunodeficiency virus (HIV), treated with clarithromycin given every 12 hours at a dose of 500 mg, were similar to those found in healthy subjects. However, the administration of higher doses necessary to treat infections caused by *Mycobacterium avium* causes plasma clarithromycin concentrations to be much greater than those observed after administration of the usual doses. In adult patients infected with HIV receiving 1 gram and 2 grams of clarithromycin per day in two divided doses, steady-state C_{max} was 2-4 µ g/ml and 5-10 µ g/ml, respectively. The elimination half-life was longer after the administration of these higher doses compared to the usual doses in healthy subjects. Elevated plasma concentrations and a longer half-life result from the non-linear course of clarithromycin pharmacokinetics.

Combination therapy with omeprazole

The pharmacokinetics of clarithromycin, given three times daily at a dose of 500 mg and omeprazole 40 mg once a day, were analysed. When clarithromycin was given every 8 hours, the mean steady-state C_{max} was around 3.8 µ g/ml, and C_{min} around 1.8 µ g/ml. The clarithromycin AUC0-8 value was 22.9 µ g*h/ml. T_{max} and half-life were 2.1 hours and 5.3 hours, respectively.

In the same study, when clarithromycin was given with omeprazole, it increased the AUC_{0-24} value and the half-life of omeprazole. The mean omeprazole AUC_{0-24} was 89% higher and the mean $T_{1/2}$ harmonic value was 34% higher when omeprazole was co-administered with clarithromycin compared to omeprazole only. In contrast, C_{max}, C_{min} and AUC_{0-8} at steady-state were 10%, 27% and 15% higher, respectively, compared to values obtained from the administration of clarithromycin with placebo.
At steady-state, 6 hours after administration, the clarithromycin concentration in the gastric mucosa was approximately 25-fold higher in the clarithromycin and omeprazole group than in the clarithromycin-only group. Six hours after dosing, the average clarithromycin concentration in the gastric tissue was approximately 2-fold higher in the case of clarithromycin with omeprazole than with clarithromycin with placebo.

Amoxicillin

Amoxicillin is stable in the acid gastric secretion and is rapidly absorbed from the gastrointestinal tract after oral administration. The presence of food does not interfere with this process. Peak plasma concentrations are obtained in about two hours, producing around 2.5 times the peak concentration resulting from comparable doses of ampicillin.

Protein binding is similar to that of ampicillin: up to 25%.
Effective levels in the cerebrospinal fluid are obtained only in the presence of inflammation and then irregularly. About 60% of an orally administered dose is excreted unchanged in the urine. It penetrates well in to purulent and mucoid sputum.

In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inuline clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally

5.3 Preclinical safety data

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 hypergastrinemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

Non-clinical data reveal no special hazard based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Clarithromycin

Acute, sub chronic and chronic toxicity studies

Studies were conducted in mice, rats, dogs and monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose was greater than the highest feasible dose for administration (5g/kg).

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 mg/kg/day for 3 months, or to 8 mg/kg/day for 6 months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of 10 monkeys receiving 400 mg/kg/day for 28 days died on treatment day 8. Yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the medicine generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage (400 mg/kg/day), some dogs and monkeys developed corneal opacities and/or edema.

Fertility, reproduction, mutagenicity and teratogenicity

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the

oestrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (po) and Sprague-Dawley (po and i.v) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg b.i.d), suggesting maternal and foetal toxicity but not teratogenicity.
Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500 mg b.i.d), starting at gestation day 20. This effect has been attributed to maternal toxicity of the medicine at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.
A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose), no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.
Mutagenicity
In mutagenic studies (Ames Test) the potential for mutagenicity of clarithromycin at drug concentrations of 25 mcg/petri plate or less was not demonstrated. At a concentration of 50 mcg, the drug was toxic for all strains tested.

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.

6. Pharmaceutical Particulars
6.1 List of Excipients

Amoxycillin 1000 mg Film coated tablets
Magnesium Stearate
Purified Talc
Croscarmellose Sodium
Cross Povidone

Colloidal Anhydrous Silica
Microcrystalline Cellulose 112
Hypromellose (As E-15)
Titanium Dioxide
Polyethylene Glycol (As 6000)
Isopropyl Alcohol and Dichloromethane.

Clarithromycin 500 mg Film coated Tablets
Microcrystalline cellulose-102
Magnesium Stearate
Talcum
Cross Carmellose Sodium
Cross Povidone
Colloidal Silicon Dioxide
Sodium Carboxymethyl Cellulose
Hydroxy propyl methyl cellulose (E-15)
Isopropyl Alcohol
Dichloromethane
Titanium Dioxide
Polyethylene Glycol (as 6000).

Esomeprazole 20 mg Tablets
Light Magnesium Oxide
Mannitol
Hydroxypropyl cellulose
Sodium Carbonate
Magnesium Stearate
Purified Talc
Cross Povidone (XL 10)
Hypromellose (E-15)
Colour: Titanium Dioxide
Iso Propyl Alcohol
Dichloromethane
Hypromellose Phthalate (HP-55)
Polysorbate 80 (Tween-80)
Dibutyl Phthalate**.**

6.2 Incompatibilities
Not Applicable

6.3 Shelf-Life
24 Months

6.4 Special Precautions for storage
Store at a temperature not exceeding 30^{o}C.
Protect from light and moisture.

6.5 Nature and Content of container
Alu – Alu Blister Pack

2 Clarithromycin 500 mg Tablets
2 amoxicillin 1000 mg Tablets
2 esomeprazole 20 mg Tablets

In a unit box Pack size: 6x7s

6.6 Special precautions for disposal and other handling
Dispose as per the local regulatory requirements.

7. Marketing Authorization Holder
GALAXY PHARMACEUTICAL LTD
Address: 1st Floor, Doctors 'Park, 3rd Parklands Avenue, P.O. Box 39107-00623, NairobiCountry: Kenya.
Tel: 020-3748551/2/3/4

Email: Info@galaxypharma.co.ke

8. Marketing Authorization Number
CTD9505

9. Date of first authorization/renewal of the authorization
06/10/2023

10. Date of revision of the text
05/05/2025