1. Name of the medicinal product

XPYLORI KIT (Combi kit of Esomeprazole Tablets 20 Mg, Clarithromycin Tablets 500 Mg & Amoxicillin Tablets USP 1000 mg)

2. Qualitative and Quantitative composition

Each kit contains: (2+2+2) individual tablets of
2 tablets of AMOXICILLIN TABLETS USP 1000 mg (A)
2 tablets of CLARITHROMYCIN TABLETS USP]00 mg (B)
2 tablets of ESOMEPRAZOLE TABLETS 20 mg (C)

(A) AMOXICILLIN TABLETS USP 1000 mg
Each film coated tablet contains:
Amoxicillin Trihydrate USP
Eq. to Amoxicillin… ..... 1000 mg
Excipients .....q.s
Colour: Titanium Dioxide BP
For the full list of excipients see section 6.1

(B) CLARITHROMYCIN TABLETS USP 500 mg
Each film coated tablet contains:
Clarithromycin U.S.P..... 500 mg
Excipients… .....q.s.
Colour: titanium dioxide BP

Excipient with known effect:
Each tablet contains lactose 52 mg.
For the full list of excipients see section 6.1

(C) ESOMEPRAZOLE TABLETS 20 mg
Each enteric coated tablet contains:
Esomeprazole magnesium
trihydrate BP Eq to
esomeprazole 20
mg
Excipients… .....qs
Colour: titanium dioxide BP, Sunset yellow FCF & Red
oxide of iron For the full list of excipients see section 6.1

3. Pharmaceutical form:

A- Amoxicillin tablets USP 1000
mg Film coated tablet
A white coloured, oblong shape, biconvex film coated tablet

B- Clarithromycin tablets 500
mg Film coated tablet
A white coloured, oblong shaped, biconvex, film coated tablet bisected on one side.

C- Esomeprazole tablets
20 mg-Enteric coated
tablet

A brown coloured, round shaped, biconvex, enteric coated tablet

4. Clinical particulars

4.1 Therapeutic indications

XPYLORI KIT is indicated for the eradication of H. pylori in patients with active chronic gastritis, gastric ulcer and duodenal ulcer.

Amoxicillin, Clarithromycin & Esomeprazole is a combination medicine that contains, Clarithromycin, an antibiotic that kills the bacteria (Helicobacter pylori), causing the infection. Esomeprazole is a proton pump inhibitor and acts by reducing the production of stomach acid. Amoxicillin is a penicillin antibiotic and bactericidal (kills the bacteria). It works by preventing the formation of bacterial cell covering (protective cell wall) necessary for their survival. Together, Amoxicillin, Clarithromycin & Esomeprazole helps to treat H. pylori infections effectively.

4.2 Posology and method of administration

One XPYLORI KIT contains two tablets of Esomeprazole (20 mg), two tablets of amoxicillin (1000 mg) and two tablets of Clarithromycin (500 mg). One pack is for 1 day of treatment.

From this specially designed pack, one tablet each of Esomeprazole, Amoxicillin, and Clarithromycin is to be taken in the morning and similarly one each in the evening. The duration of therapy recommended is for 7-14 days.

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

4.3 Contraindications

Hypersensitivity to Esomeprazole, Clarithromycin and Amoxicillin or to any of the excipients listed in section 6.1.

Esomeprazole

Esomeprazole should not be used concomitantly with nelfinavir.

Clarithromycin

Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine), oral midazolam and lomitapide is contraindicated, as this may result in ergot toxicity.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and torsades de pointes.

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes.

Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated. Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis. As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval). Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

Amoxicillin

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

monobactam).

4.4 Special warnings and precautions for use

Amoxicillin, Clarithromycin & Esomeprazole should not be used in patients with arrhythmias or taking antiarrhythmic agents, as it may lead to prolonged QT intervals, which can be life-threatening. While using Amoxicillin, Clarithromycin & Esomeprazole, if you notice severe or prolonged diarrhoea, vomiting food or blood, black stools, unexplained weight loss, or symptoms of liver disease (jaundice (yellowing of the skin), loss of appetite, dark urine, or itching), stop the medication and consult a doctor immediately. Besides, if you notice skin rashes or lesions, especially on sun-exposed skin, stop the treatment and immediately consult a doctor. Amoxicillin, Clarithromycin & Esomeprazole increases the risk of Clostridium difficile-associated diarrhoea (inflammation of the large intestine due to Clostridium infection). Amoxicillin, Clarithromycin & Esomeprazole may increase the risk of fractures, cause liver impairment, and impair the absorption of vitamin B12 in the body when used for prolonged periods.

4.5 Interaction with other medicinal products and other forms of interaction <u>Esomeprazole</u>

Effects of esomeprazole on the pharmacokinetics of other medicinal products Protease inhibitors

Increased gastric pH or inhibition of CYP 2C19 during omeprazole treatment may change the absorption of the protease inhibitors. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approx. 75% decrease in AUC, Cmax and Cmin). Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, Cmax and Cmin by 36– 39 % and mean AUC, Cmax and Cmin for the pharmacologically active metabolite M8 was reduced by 75-92%.
For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd).

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 such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Omeprazole increases the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients and TDM of digoxin should be reinforced.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with other medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these active substances 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 with diazepam resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

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

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC by 15% and 41%, respectively.

Cilostazol Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively

Cisapride

Concomitant administration of 40 mg esomeprazole resulted in a 32% increase in AUC and a 31% prolongation of elimination half-life (t1/2) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Warfarin

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

Clopidogrel Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o.daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggression by an average of 14%.

Clarithromycin

The use of the Cisapride, pimozide, domperidone, astemizole and terfenadine is strictly contraindicated due to the potential for severe drug interaction effects:

Ergot alkaloids: co-administration causesvasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these ergot alkaloids is contraindicated.

Oral midazolam: The AUC of midazolam increases 7-fold following the administration of oral midazolam. The concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis.

Effects of other medicinal products on clarithromycin

CYP3A inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) may induce the metabolism of clarithromycin leading to reduced efficacy.

Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin;

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 active 14-OH-clarithromycin metabolite. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH clarithromycin, were increased.

Fluconazole

Concomitant administration of fluconazole and clarithromycin led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively.

Ritonavir

Concomitant administration of ritonavir and clarithromycin resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77%. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Dosages therefore for clarithromycin need be adjusted for patients with renal impairment.

Effect of clarithromycin on other medicinal products CYP3A-based interactions

Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids.

Antiarrhythmics

There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide.

Oral hypoglycaemic agents/Insulin
With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly.
Direct acting oral anticoagulants
Dabigatran and edoxaban are substrates for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co administered with these agents particularly to patients at high risk of bleeding.
Sildenafil, tadalafil, and vardenafil
Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure as they are metabolized by CYP3A4 which would be inhibited by clarithromycin.
Theophylline, carbamazepine
There is statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either is given concomitantly with clarithromycin.
Tolterodine
Inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.
Triazolobenzodiazepines
(e.g. alprazolam, midazolam, triazolam)
When IV midazolam was co-administered with clarithromycin tablets, midazolam AUC was increased 2.7-fold. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. There have been post-marketing reports of somnolence and confusion with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.
Amoxicillin
Oral anticoagulants
There are cases of increased INR in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or INR should be carefully monitored with the addition or withdrawal of amoxicillin.
Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin results in increased and prolonged blood levels of amoxicillin
Allopurinol
Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Tetracyclines
Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.
Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.
4.6 Fertility, pregnancy and lactation Pregnancy

Caution should be exercised when prescribing esomeprazole to pregnant women. The safety of clarithromycin for use during pregnancy has not been established. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

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. The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin. Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility. In the rat, fertility studies with clarithromycin have not shown any evidence of harmful effects. There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

Xpylori kit 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.

4.8 Undesirable effects

The common side effects of Xpylori Kit include headache, abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting, dysgeusia, rash, hyperhidrosis, urticaria, pruritus. The uncommon side effects include insomnia, dizziness, somnolence, paraesthesia, dry mouth, increased liver enzymes, urticaria, decreased appetite

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'.

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 that the ingestion of large amounts of clarithromycin can

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

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.

Clarithromycin

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide ATC code: J01FA09

Mechanism of action

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The MIC of clarithromycin are generally two fold lower than MICs of erythromycin.

Amoxicillin

Pharmacotherapeutic group: penicillins with extended spectrum; ATC code: J01CA04

Mechanism of action

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

5.1 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

Clarithromycin

Absorption

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract after oral administration. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite.

Metabolism

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing.

Distribution

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels. Clarithromycin also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

Excretion

At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

Amoxicillin

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (Tmax) is approximately one hour. In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as Cmax and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 1/kg.

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

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

Amoxicillin has been shown to cross the placental barrier.

Biotransformation

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

Elimination

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

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

5.2 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.

Clarithromycin

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg). In repeated dose studies, toxicity was related to dose, duration of treatment and species. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. Fertility, Reproduction and Teratogenicity Studies performed in rats at oral doses up to 500 mg/kg/day (highest dose associated with overt renal toxicity) demonstrated no evidence for clarithromycin-related adverse effects on male fertility. Fertility and reproduction studies in female rats have shown that a daily dosage of 150 mg/kg/day (highest dose tested) caused no adverse effects on the oestrus cycle, fertility, parturition and number and viability of offspring.

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

A- Esomeprazole

- Magnesium Oxide Light
- Mannitol Pyrogen Free
- Microcrystalline Cellulose
- Croscarmellose Sodium
- Polyvinyl Pyrrolidone (PVPK 30)
- Methylene Dichloride
- Ethyl Cellulose
- Magnesium Stearate
- Colorcoat Sc4s (White)
- Iso Propyl Alcohol
- Colorcoat Ec4s-B (Brown)

B. Clarithromycin

- Lactose
- Croscarmellose Sodium
- Microcrystalline Cellulose
- Sodium Lauryl Sulphate
- Polyvinyl Pyrrolidone (PVPK 30)
- Iso Propyl Alcohol
- Colloidal Silicon Dioxide
- Magnesium Stearate
- Polacrilin Potassium
- Hydroxy Propyl Methyl Cellulose
- Methylene Dichloride
- Ethyl Cellulose
- Talcum
- Poly Ethylene Glycol
- Propylene Glycol
- Titanium Dioxide

C. Amoxicillin

- Microcrystalline cellulose
- Crospovidone
- Purified talc
- Colloidal silicon Dioxide
- Magnesium stearate
- Potassium Polacrilin
- Hydroxy Propyl Methyl Cellulose
- Titanium Dioxide
- Polyethylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Combi kit of Esomeprazole Tablets 20 mg, Clarithromycin Tablets 500 mg & Amoxicillin Tablets USP 1000 mg. 2 Tablets of each molecule in one Alu-Alu blister pack. Such 1 x 7 packs in a combi pack with an insert.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 Marketing authorisation holder

Manufactured in India by:
HEALTHCARE FORMULATIONS PVT. LTD
C/8, Sardar Estate, Ajwa Road,
Vadodara – 390 019, Gujarat,
Indi

Manufactured For & Marketed by:
KRISHNA CHEMISTS LTD.
P.O. BOX 3328-00506
Nairobi, Kenya.

8 Marketing authorisation number(s)

H2025/CTD9330/15528

9 Date of first authorisation/renewal of the authorisation

13/12/2024

10 Date of revision of the text

2030 July 17