SUMMARY OF PRODUCT CHARACTERISTICS

3D KIT H. PYLORI KIT

1. **Product Description**
   Name of Medicinal Product
   3D Kit H. Pylori Kit

2. **Qualitative and Quantitative Composition**
   Each Kit contains:
   1. **Amoxicillin Tablets 1000 mg**
      Each Film coated Tablet Contains:
      Amoxicillin Trihydrate BP
      Eq. to Amoxicillin 1000 mg
      Excipients q.s.
   2. **Levofloxacin Tablets USP 500 mg**
      Each Film coated Tablet Contains:
      Levofloxacin hemihydrates USP
      Eq. to Levofloxacin 500 mg
      Excipients q.s.
   3. **Rabeprazole Tablets 20 mg**
      Each Enteric Coated Tablets Contains:
      Rabeprazole sodium BP
      Eq. to Rabeprazole 20 mg
      Excipients q.s.

      For full list of excipients, see section 6.1

3. **Pharmaceutical Form**

   Amoxicillin Tablets 1000 mg: Film Coated Tablet

   Levofloxacin Tablets USP 500 mg: Film Coated Tablet

   Rabeprazole Tablets 20 mg: Enteric Coated Tablet

4. **Clinical Particulars**

4.1 Therapeutic Indications and Uses

3D Kit H. Pylori Kit is indicated in the eradication of H. pylori in active chronic gastritis, duodenal and gastric ulcers.

4.2 Posology and Method of Administration

3D Kit H. Pylori Kit contains 7 kits to be taken in 7 days.
Each one-day kit contains a morning kit and an evening kit.
Both the Morning and Evening kits contain 1 tablet of Amoxicillin 1000mg, 1 tablet of Levofloxacin 500 mg and 1 tablet of Rabeprazole 20 mg.
The recommended therapy is for 7-14 days as per the Physicians advice.

4.3 Contraindications

- Hypersensitivity to the active substances, or to any of the excipients.

Amoxicillin

- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin.

Levofloxacin

- Hypersensitivity to other quinolones
- In patients with epilepsy
- In patients with history of tendon disorders related to fluoroquinolone administration.
- In children or growing adolescents
- During pregnancy
- In breast-feeding women

Rabeprazole

- Hypersensitivity to derivatives of benzimidazoles
- In pregnancy and during breast feeding.

4.4 Special Warnings and Precautions for Use

Amoxicillin

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

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs,

amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin to amoxicillin in accordance with official guidance.

This presentation is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant S. pneumoniae.

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

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemouspustulosis (AGEP). This reaction requires Co-Amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

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

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

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Levofloxacin

Methicillin-resistant *S.* aureus is very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Bronchitis when these infections have been adequately diagnosed.

Resistance to fluoroquinolones of E. coli – the most common pathogen involved in urinary tract infections – varies across the European Union.

Prescribers are advised to take into account the local prevalence of resistance in *E. coli* to fluoroquinolones.

Inhalation Anthrax: Use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and,

as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substance that lower the cerebral seizure threshold, such as theophylline. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted in patients with renal impairment.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose. Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Rabeprazole

Symptomatic response to therapy with Rabeprazole tablet does not exclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole tablet. Patients on long term treatment (particularly those treated for more than a year) should be kept under regular surveillance. Because there are no clinical data on the use of Rabeprazole tablet in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole tablet is first initiated in such patients. A risk of cross-hypersensitivity reactions with other proton pump inhibitors or with substituted benzimidazoles cannot be excluded. There have been post marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since rabeprazole products are marketed. In the majority of the cases where an alternative

etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole

4.5 Interactions with other medicinal products and other forms of interaction

Amoxicillin

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

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

Probenecid: Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Levofloxacin

Effect of other medicinal products on levofloxacin

Iron salts, zinc-salts, magnesium- or aluminium-containing antacids, didanosine: Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with levofloxacin tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cautions such as iron salts, zinc-salts or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents should not be taken 2 hours before or after Levofloxacin 250mg Film-coated Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate: The bioavailability of Levofloxacin 250mg Film-coated Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the Levofloxacin 250mg Film-coated Tablets administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs: No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine: Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance. Caution should be exercised when levofloxacin is co-administered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Effect of levofloxacin on other medicinal products

Ciclosporin: The half-life of cyclosporine was increased by 33% when co administered with levofloxacin.

Vitamin K antagonists: Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.

Drugs known to prolong QT interval: Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

Rabeprazole

Cytochrome P450 System

Rabeprazole, a proton pump inhibitor (PPI), like other members of this class of medicines, is metabolised via hepatic cytochrome P450 (CYP450) system drug metabolism. Specifically, studies with human liver microsomes, show that rabeprazole is metabolised by CYP3A4 and CYP2C19 isoenzymes.

In studies conducted in healthy subjects it is shown that rabeprazole doesn't interact in a clinically significant way with warfarin, phenytoin, theophylline, or diazepam and the other drugs which are metabolised by CYP450 system.

Antibacterial combination therapy

Combination therapy performed with the antimicrobial agents: four-arm crossover study, in 16 healthy volunteers with 40 mg of rabeprazole, 1000 mg, amoxicillin, 500 mg clarithromycin or a combination with these third agents, i.e., rabeprazole, amoxicillin and clarithromycin (RAC). During the combination therapy, clarithromycin and amoxicillin AUC and Cmax values were found similar when compared with monotherapy. When compared with the data obtained during monotherapy, AUC and Cmax values of rabeprazole increased 11% and 34% and AUC and Cmax values of 14-hydroxy-clarithromicycin (active clarithromycin metabolite) increased 42% and 46%. This increase to be exposed to rabeprazole and 14- hydroxyl-clarithromycin was not found important.

Interferences due to inhibition of gastric acid secretion

Rabeprazole produces a profound and long-lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole with ketoconazole (decreasing of 30 %) or itraconazole (increasing of 22 %) may result in a significant decrease in antifungal plasma levels. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.

Antacids

In clinical studies, antacids were used concomitantly with the administration of rabeprazole. Also, in a specific drug-drug interaction study, no interaction with liquid antacids (aluminium hydroxide gel or magnesium hydroxide) was observed.

Cyclosporine

Human liver microsomes are used in vitro (in a laboratory) incubations, rabeprazole, cyclosporine metabolism 62 micromole with an IC50 inhibited revealed that, said this concentration for 14 days, 40 mg rabeprazole administered in healthy volunteers detected Cmax 50 times higher. This degree of inhibition equivalent to that provided by at concentrations close to omeprazole.

Atazanavir

Co-administration of atazanavir 300mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

4.6 Pregnancy and Lactation

Pregnancy

Amoxicillin: Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Levofloxacin: There is limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women.

Rabeprazole: There are no clinical data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole, although foetal-placental transfer occurs in rats.

Rabeprazole gastro-resistant tablets are contraindicated during pregnancy.

Lactation

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

Levofloxacin: Is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be in breast-feeding women.

Rabeprazole: It is not known whether rabeprazole is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole is however excreted in rat mammary secretions. Therefore, Rabeprazole tablet should not be used during breast feeding.

4.7 Effects on Ability to Drive and Use Machines

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

Levofloxacin: Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Rabeprazole: Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole tablet would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 Undesirable Effects

Amoxicillin

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leukopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and PT	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea and Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known

Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Skin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria	Not known

Levofloxacin

System organ class	Common	Uncommon	Rare	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	Anaphylactic shock

				Anaphylactoid shock (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis

Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	

Rabeprazole

System organ class/ Undesirable effect	**Frequency**
Infections and infestations	
Infections	Common
Blood and the lymphatic system	
Neutropenia, leucopoenia, thrombocytopenia, leucocytosis	Rare
Immune system disorders	
Acute systemic allergic reactions (e.g. hypotension and dyspnoea)	Rare
Metabolism and nutrition disorders	
Anorexia	Rare
Hyponatremia	not known
Psychiatric disorders	
insomnia	Common
Nervousness	Uncommon
Depression	Rare
Confusion	Unknown
Nervous system disorders	
Headache, dizziness	Common
Somnolence	Uncommon
Vascular disorders	

System organ class/ Undesirable effect	**Frequency**
Peripheral oedema	Unknown
Eye disorders	
Visual disturbance	Rare
Respiratory, thoracic and mediastinal disorders	
Cough, pharyngitis, rhinitis	Common
Bronchitis, sinusitis	Uncommon
Gastrointestinal disorders	
Diarrhoea, vomiting, nausea Abdominal pain Constipation, flatulence	Common
Dyspepsia, dry mouth, eructation	Uncommon
Gastritis, stomatitis, taste disturbance	Rare
Hepato-biliary disorders	
Hepatitis, jaundice, hepatic encephalopathy	Rare
Skin and subcutaneous tissue disorders	
Rash, erythema	Uncommon
Pruritus, sweating, bullous reactions	Rare
Erythema multiforme, toxic epidermal necrolysis (TEN) Stevens-Johnson syndrome (SJS)	Very rare
Musco-skeletal, connective tissue and bone disorders	
Non-specific pain, back pain	Common
Myalgia, leg cramps, arthralgia	Uncommon
Renal and urinary disorders	
Urinary tract infection	Uncommon
Interstitial nephritis	Rare
Reproductive system and breast disorders	
Gynecomastia	Unknown
General disorders and administration site conditions	
Asthenia, influenza-like illness	Common
Chest pain, chills, pyrexia	Uncommon
Investigations	
Increased hepatic enzymes	Uncommon
Weight increase	Rare

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 Pharmacovigilance Electronic Reporting System (PvERS)

https://pv.pharmacyboardkenya.org/

4.9 Overdose

Amoxicillin:

Symptoms and signs of overdose: Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed Convulsions may occur in patients with impaired renal function or in those receiving high doses. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.

Treatment of intoxication: Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin can be removed from the circulation by haemodialysis.

Levofloxacin: According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions. CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

Rabeprazole: Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Amoxicillin: Pharmacotherapeutic group: beta-lactamase inhibitors (beta-lactam antibiotic). ATC code: J01CR02.

Levofloxacin: Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones, ATC code: J01MA12

Rabeprazole: Pharmaceutical group: proton pump inhibitor for peptic ulcer and gastro-oesophageal reflux disease (GORD). ATC code: A02BC04

Mode of Action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active substance ofloxacin. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV. The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Rabeprazole belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by

the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump) The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteine on the proton pump.

5.2 Pharmacokinetic Properties

Absorption

Amoxicillin is fully dissociated in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Absorption is optimized when taken at the start of a meal. Following oral administration, approximately 70% of the drug is bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1h. The absolute bioavailability is approximately100%. Food has little effect on the absorption of levofloxacin.

Rabeprazole tablet is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring +3.5 hours after a 40 mg dose. Peak plasma concentrations (Cmax) and AUC are linear over the dose range of 10mg to 40mg. Absolute bioavailability of an oral 40mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally, the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is +1 hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. Neither food nor the time

of day of administration of the treatment affects the absorption of rabeprazole.

Distribution

About18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin. 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.

Approximately 30 – 40% of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

Rabeprazole is approximately 97% bound to human plasma proteins.

Biotransformation and Elimination

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. The major route of elimination for amoxicillin is via the kidney. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 – 8 h). Excretion is primarily by the renal route (>85% of the administered dose. There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Rabeprazole is metabolised through the cytochrome P450 (CYP450) hepatic drug z system. In vitro studies with human liver microsomes indicated that rabeprazole is metabolised by isoenzymes of CYP450 (CYP2C19 andCYP3A4). Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5)

and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in feces.

5.3 Preclinical Safety Data

Amoxicillin: Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue. Carcinogenicity studies have not been conducted.

Levofloxacin: Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development. Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity. Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential. Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photo-carcinogenicity study. In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

Rabeprazole: Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data. Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6. Pharmaceutical Properties

6.1 List of Excipients

Amoxicillin

Microcrystalline Cellulose

P.V.P K-30

Sodium Starch Glycolate

Colloidal Silicon Dioxide

Magnesium Stearate

Purified Talc

Isopropyl Alcohol

Methylene Chloride

Titanium Dioxide

HPMC

Levofloxacin

Maize Starch

Microcrystalline cellulose

Maize Starch

P.V.P K-30

Purified water

Purified Talc

Magnesium Stearate

Sodium Starch Glycolate

Colloidal Anhydrous Silica

Isopropyl Alcohol

Methylene Chloride

Tween -80

PEG -6000

HPMC

Titanium Di-oxide

Sunset Yellow supra

Rabeprazole

Mannitol

Sodium Bicarbonate

Povidone K -30

Iso –propyl alcohol

Purified Talc

Magnesium Stearate

Colloidal Anhydrous silica

Croscarmellose sodium

Methylene Dichloride

Titanium dioxide

Red oxide of Iron

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container

Amoxicillin 2 Tablets are packed in one Alu-Alu blister.

Levofloxacin 2 Tablets are packed in one Alu-Alu blister.

Rabeprazole 2 Tablets packed in one ALU-ALU blister.

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.

7. Marketing Authorization Holder

NATIONAL PHARMACY LIMITED
COLCHESTER PARK
P.O. BOX 17843-00500
NAIROBI

8. Marketing Authorization Number(s)

H2026/CTD10837/23368

9. Date of First Authorization/Renewal of the Authorization

17.12.2025

10. Date of Revision of the Text

18th August 2026