Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

NEXILEV KIT

2. Qualitative and quantitative composition

1. Esomeprazole

Each Enteric coated tablet contains Esomeprazole Magnesium Trihydrate equivalent to Esomeprazole 40mg

Excipients with known effects

Each Esomeprazole 40mg Enteric coated tablet contains Lactose

2. Levofloxacin Tablet

Each film coated tablet contains Levofloxacin Hemihydrate equivalent to Levofloxacin 500mg

Excipients with known effects

Each Levofloxacin 500mg film coated tablet contains Isopropyl alcohol

3. Amoxicillin Tablet

Each film coated tablet contains Amoxicillin Trihydrate equivalent to Amoxicillin 1000mg

Excipients with known effects

Each Amoxicillin 1000mg Tablet contains Isopropyl Alcohol.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Amoxicillin Tablet USP 500 mg

Brown coloured elongated biconvex film coated tablets breakline on one side and plain on another side

Levofloxacin Tablet USP 500 mg

Orange colored oblong shaped slightly biconvex tablets.

Esomeprazole Tablet 40 mg

Yellow coloured, circular shaped slightly biconvex film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

NEXILEV KIT is indicated in the eradication of H. pylori in active chronic gastritis, duodenal and gastric ulcers.

4.2 Posology and method of administration

Adult Patient:
NEXILEV KIT contains 7 kits to be taken in 7 days.
Each one-day kit contains a morning kit and an evening kit.
Morning kit contains 1 tablet of Esomeprazole 40mg and 2 tablets of Amoxicillin 500mg and the evening kit contains 1 tablet of Levofloxacin and 2 tablets of Amoxicillin.
The recommended therapy is for seven days and may be extended as per the Physicians advice.

Pediatric and Adolescent: Since this product has not been studied in the adolescent and pediatric population this product is not recommended in this age group.

4.3 Contraindications

1. A history of allergic reaction to any of the penicillin‟s and infections caused by penicillinase producing organism are contraindicated.
2. Levofloxacin tablets must not be used:
    - in patients hypersensitive to levofloxacin, or other quinolones or any of the excipients listed in section 6.1
    - 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.
3. 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 NEXILEV KIT, carefully inquire from the patient concerning hypersensitivity to penicillinS cephalosporin and other allergens. Serious and occasionally fatal hypersensitivit 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, cautionshould be taken when using fluoroquinolones, including levofloxacin, in these populations

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.

Effect of other medicinal products on levofloxacin
Iron salts, zinc salts, magnesium- or aluminium-containing antacid, didanosines
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 cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after Levofloxacin tablet administration (see section 4.2). Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate
The bioavailability of Levofloxacin 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 administration (see section 4.2).

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 coadministered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

When administered concurrently, the following Drugs may interact with 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.

Levofloxacin
Pregnancy

There are 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 (see section 5.3). 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 (see section 4.2 and 5.3).

Breast-feeding

The product 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 the experimental data suggests risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

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.

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).

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

Levofloxacin

System organ class	**Common 21/100 to < 1/10)**	**21/1,000 to <1/100)**	**Rare 21/10,000 to < 1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations		Fungal infection including Candidia infection Pathogen resistance		Genital moniliasis
Reproductive System				Vaginitis

Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Pancytopenia Neutropenia	Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedma 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 reaction (with e.g. hallucinations, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsions (see section 4.3 and 4.4) neuropathy (see Parasethesia	Peripheral sensory section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including
				anosmia Dyskinesia Extrapyramidal disorder Ageusia Synocope Benign intracranial hypertension Hypoaesthesia
Eye disorders			Visual disturbances Transient vision such as blurred vision (see section 4.4)	loss (see section 4.4)
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired

Cardiac disorders			Tachycardia Palpitation	Ventricular tachycardia, which may result in cardiac arrest Venticular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9)
Vascular disorders	Applies to i.v. form only: Phlebitis		Hypotension	
Respiratory, thoracic and medistinal		Dyspnoea		Bronchospasm Pneumonitis
disorders				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, CGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily with severe underlying diseases (see section 4.4) Hepatitis

Skin and subcutaneous tissue disorders		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon)	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and
			Muscle weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	4.4) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions	Applies to i.v. form Asthenia only: Infusion site reaction (pain, reddening)		Pyrexia	Pain (including pain in back, chest, and extremities)

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.

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 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 include 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.

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.

Levofloxacin

Pharmacotherapeutic group:
ATC code: Quinolone antibacterials - Fluoroquinolones
J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

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).

Mechanism of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Amoxicillin

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.

Levofloxacin

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 – 2 h. The absolute bioavailability is 99 - 100%.

Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage

regimen.

Distribution

Approximately 30 – 40% of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

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).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/- 29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

Special populations

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 m dose

Cl_{cr} [ml/min]	<20	20 - 49	50-80
Cl_R [ml/min]	13	26	57
$T_{1/2}$ [h]	35	27	9

Elderly subjects

There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences

Separate analysis for male and female subjects showed a small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

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 hypergastrinaemia 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.

Levofloxacin

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on foetuses 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 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 photo mutagenicity 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.

6. Pharmaceutical particulars

6.1 List of excipients

Esomeprazole
Light Magnesium oxide
Mannitol –H
Microcrystalline cellulose
Maize starch
Lactose
Povidone
Iso –propyl alcohol
Purified Talc
Magnesium Stearate
Colloidal Anhydrous silica
Crosscarmelose sodium
Titanium dioxide
Color Iron oxide yellow
Methylene Dichloride

Levofloxacin
Maize Starch
Microcrystalline cellulose
Lactose
Maize Starch
Povidone
Purified water
Purified Talc
Magnesium Stearate
Sodium Starch Glycolate
Colloidal Anhydrous Silica
Isopropyl alcohol
Titanium dioxide
Sunset yellow
Methylene Chloride

HPMC E15

Amoxicillin
HPMC E 15
P.V.P K-30
Sodium Starch Glycolate
Magnesium Stearate
Purified Talc
Isopropyl Alcohol
Methylene Chloride
Titanium dioxide
Red oxide of Iron

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage:
Store below 30℃
Protect from moisture.

6.5 Nature and contents of container
Alu -Alu strip pack.
2 levofloxacin tablets USP 500 mg
2 amoxicillin tablets BP 1000 mg
2 esomeprazole tablets 40 mg
In a baby carton with a package insert and 7 such packs in a mono carton.

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

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
PHARMAKEN LTD.
Address: P.O Box 95625-80106 Nairobi, Kenya

Manufacturing site address:
GLOBAL PHARMA HEALTHCARE
Address: A-9, SIDCO PHARMACEUTICAL COMPLEX, Alathur, Thiruporur- 603110. CHENNAI, INDIA.

8. Marketing authorization number
CTD9365

9. Date of first registration

29/06/2022

10. **Date of revision of the text:**
    17/09/2023
11. **Dosimetry:**
    Not Applicable

12. **Instructions for Preparation of Radiopharmaceuticals:**
    Not Applicable