Summary of Product Characteristics for Pharmaceutical Products

1.Name of the medicinal product

Esoflax Kit (Combi-pack Of Esomeprazole Tablets, Amoxicillin Tablets & Levofloxacin Tablets)

2.Qualitative and quantitative composition

Each Combi pack contains
Esomperazole Magnesium Delayed Release Tablets 40 Mg (2 Tablets)
Each Enteric Coated Tablet contains
Esomeprazole Magnesium Trihydrate U.S.P.
Eq to Esomeprazole.....40 mg

Amoxicillin Tablets Usp 1000 Mg (2 Tablets)
Each film coated tablet contains Amoxicillin Trihydrate B.P.
Eq. to Amoxicillin.....1000 mg

Levofloxacin Tablets Usp 500 Mg (2 Tablets)
Each film coated tablet contains Levofloxacin Hemihydrate U.S.P.
Eq. To levofloxacin .....500 mg

3. Pharmaceutical form

Esomperazole Magnesium Delayed Release Tablets 40 Mg: Enteric Coated Tablets
Amoxicillin Tablets Usp 1000 Mg: Film Coated Tablets
Levofloxacin Tablets Usp 500 Mg: Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Esomeprazole Tablets are indicated in adults for:
Gastro esophageal Reflux Disease (GERD)
Treatment of erosive reflux esophagitis
Long-term management of patients with healed esophagitis to prevent relapse
Symptomatic treatment of gastro esophageal reflux disease (GERD)
In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and
healing of Helicobacter pylori associated duodenal ulcer and
Prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.
Patients requiring continued NSAID therapy
healing of gastric ulcers associated with NSAID therapy.
Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
Treatment of Zollinger Ellison Syndrome
Esomeprazole Tablets are indicated in adolescents from the age of 12 years for:

Gastroesophageal Reflux Disease (GERD)
Treatment of erosive reflux esophagitis
Long-term management of patients with healed esophagitis to prevent relapse
Symptomatic treatment of gastro esophageal reflux disease (GERD)
In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori

(B) AMOXICILLIN TABLETS USP 1000 MG:

Amoxicillin Tablets is indicated for the oral treatment of the following bacterial infections caused by amoxicillin-susceptible gram-positive and gram-negative pathogens
Infections of the upper respiratory tract, including infections of the ears, nose and throat: Acute otitis media, acute sinusitis and bacterial pharyngitis
Infections of the lower respiratory tract: Acute exacerbation of chronic bronchitis, community-acquired pneumonia
Infections of the lower urinary tract: Cystitis
Prophylaxis of endocarditis in patients at risk i.e. surgery in the oral cavity or upper airways Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents. Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Levofloxacin Tablets is indicated in adults for the treatment of the following infections:

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections

For the above-mentioned infections Levofloxacin Tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- Pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis
- Uncomplicated cystitis
- Inhalation Anthrax: post exposure prophylaxis and curative treatment

Levofloxacin Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Posology
Adults
Gastroesophageal Reflux Disease (GERD)
treatment of erosive reflux esophagitis 40 mg once daily for 4 weeks.
An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.
long-term management of patients with healed esophagitis to prevent relapse 20 mg once daily.

- symptomatic treatment of gastroesophageal reflux disease (GERD)
20 mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. An on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.
In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and
- healing of Helicobacter pylori associated duodenal ulcer and - prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers
20 mg Esomeprazole Tablets with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.
Patients requiring continued NSAID therapy
healing of gastric ulcers associated with NSAID therapy:
The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.
prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:
20 mg once daily.
Treatment of Zollinger Ellison Syndrome
The recommended initial dosage is Esomeprazole Tablets 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.
Method of administration
For oral administration.

(B) AMOXICILLIN TABLETS USP 1000 MG:

The dosage of amoxicillin is dependent on age, bodyweight and renal function of the patient, on the seriousness and localisation of the infection and on the expected or proved causative agent. The tablets can be used in two ways. First disperse in water, then drink, or take directly with water. The tablets may be broken to ease the swallowing.
Amoxicillin Tablets can be taken either before, during or after meals. Treatment of infections: In general the therapy should be continued for 2 to 3 days following the disappearance of symptoms. In betahaemolytic streptococcal infections the duration of therapy should be at least 10 days in order to achieve eradication of the organism.
Parenteral therapy is indicated if the oral route is considered impracticable or unsuitable, and particularly for the urgent treatment of severe infection
Adults (including elderly) and children above 12 years of age.
The usual dosage covers a range from 750 mg to 3g amoxicillin daily in divided doses. In some areas 1500 mg amoxicillin daily in divided doses are recommended as the upper usual dose.
Special dosage recommendation acute exacerbation of chronic bronchitis in adults: 2 x 1 g per day Dosage in impaired renal function
The dose should be reduced in patients with severe renal function impairment. In patients with a renal clearance of less than 30 ml/min an increase in the dosage interval or a reduction in the subsequent doses is recommended. Short course treatments with a single dose of 3 g cannot be given in case of renal failure. Method of administration
For oral administration.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Levofloxacin Tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.
Treatment time
The duration of therapy varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin Tablets should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.
The following dose recommendations can be given for Levofloxacin Tablets:
Dosage in patients with normal renal function
(Creatinine clearance > 50 ml/min)

Indication	Daily dose regimen (according to severity)	Duration of treatment (according to severity)
Acute bacterial sinusitis	500 mg once daily	10 - 14 days
Acute bacterial exacerbations of chronic bronchitis	500 mg once daily	7 - 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Pyelonephritis	500 mg once daily	7 - 10 days
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Uncomplicated cystitis	250 mg once daily	3 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500 mg once or twice daily	7 - 14 days
Inhalation Anthrax	500 mg once daily	8 weeks

Special Populations
Impaired renal function (creatinine clearance ≤ 50 ml/min)

Creatinine clearance	Dosage regimen 250 mg/24 h	500 mg/24 h	500 mg/12 h
	First dose: 250 mg	First dose: 500 mg	First dose: 500 mg
50-20 ml/min	Then:125 mg/24h	Then: 250 mg/24 h	Then:250 mg/12 h
19-10 ml/min	Then: 125 mg/48 h	Then: 125 mg/24 h	Then:125 mg/12 h
< 10 ml/min (including haemodialysis and CAPD)1	Then: 125 mg/48 h	Then: 125 mg/24 h	Then:125 mg/24 h

1 No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
Impaired liver function
No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.
Elderly population
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function Paediatric population
Levofloxacin is contraindicated in children and growing adolescents.

Method of administration
Levofloxacin Tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dose. The tablets may be taken during meals or between meals. Levofloxacin Tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents), and sucralfate administration since reduction of absorption can occur.

4.3 Contraindications

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed in formulation of the same.
Esomeprazole should not be used concomitantly with nelfinavir.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Amoxicillin Tablets is contraindicated in patients with:

- Hypersensitivity to penicillin; a cross-allergy to β-lactams such as cephalosporins should be taken into account.
- Hypersensitivity to any of the other ingredients in the formulation of product.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Levofloxacin Tablets must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients
- 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.

4.4 Special warnings and precautions for use

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole Tablets may alleviate symptoms and delay diagnosis.
Long term use
Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
On demand treatment
Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.
Helicobacter pylori eradication
When prescribing esomeprazole for eradication of Helicobacter pylori, possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.
Gastrointestinal infections
Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.
Absorption of vitamin B12
Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sunexposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Esomeprazole Tablets. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

Sucrose

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillin and cephalosporins. The possibility of cross-hypersensitivity (10 % - 15 %) with cephalosporins should be taken into account. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of hypersensitivity to beta-lactam antibiotics.

Patients suffering from severe gastrointestinal disturbances with diarrhoea and vomiting should not be treated with Amoxicillin Tablets, due to the risk of reduced absorption. In these cases a parenteral treatment with amoxicillin is advisable.

Amoxicillin Tablets should be used with caution in patients with allergic diathesis and asthma.

In patients with renal impairment the excretion of amoxicillin will be delayed and, depending on the degree of the impairment, it may be necessary to reduce the total daily dosage

The prolonged use of amoxicillin may occasionally result in an overgrowth of non-susceptible organisms or yeasts. Patients should therefore carefully be watched for super infections.

The occurrence of anaphylactic shock and other severe allergic reactions is rare following the oral administration of amoxicillin. However, if such reactions occur, appropriate emergency treatment measures must be taken: I.V. administration of epinephrine, followed by antihistaminic drugs, volume substitution and administration of glucocorticoids. Patients should be kept under close observation, and further therapeutic measures (artificial respiration, oxygen) should be administered as required.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Methicillin-resistant Staphylococcus aureus (MRSA)

Methicillin-resistant S. aureus are 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 (see section 4.2). 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 (see section 4.8). 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 Tablets should be stopped immediately and appropriate treatment initiated without delay (e.g. oral metronidazole or vancomycin). Medicinal products inhibiting the peristalsis 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 (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances 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 Tablets should be adjusted in patients with renal impairment.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour- sometimes after only a single dose of levofloxacin. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

QT interval prolongation

Caution should be taken when using fluoroquinolones, 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. hypokalemia, hypomagnesemia)

cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately. Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.
Levofloxacin may inhibit the growth of Mycobacterium tuberculosis and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Effects of esomeprazole on the pharmacokinetics of other drugs
Protease inhibitors
Omeprazole 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. 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 (approximately 75% decrease in AUC, Cmax and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. 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%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.
For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).
Methotrexate
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In highdose 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. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients.
Therapeutic drug monitoring of digoxin should then be reinforced.
Medicinal products metabolized 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.
Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC_{τ} 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
In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (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 (see also section 4.4).
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 aggregation by an average of 14%.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction

Amoxicillin and quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Naproxen or rofecoxib

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolized by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Paediatric population

Interaction studies have only been performed in adults.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Concomitant use not recommended

Allopurinol

Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions and is therefore not advised.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin. A dose adjustment of digoxin may be necessary.

Disulfiram

Simultaneous administration of disulfiram is contraindicated.

Anticoagulants

Concomitant administration of amoxicillin and anticoagulants, from the coumarin class, may prolong thebleeding time. A dose adjustment of anticoagulants may be necessary.

Probenicid

By inhibiting the renal elimination of amoxicillin the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Other antibiotics

In general amoxicillin should not be combined with bacteriostatic chemotherapeutics/antibiotics (like tetracyclines, macrolids, sulfonamids or chloramphenicol), because in vitro antagonism is observed. When used simultaneously with aminoglycosides a synergistic effect may occur.

Methotrexate

Interaction between amoxicillin and methotrexate leading to methotrexate toxicity has been reported. Serum methotrexate levels should be closely monitored in patients who receive amoxicillin and methotrexate simultaneously. Amoxicillin decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

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 cations 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 Tablets administration. 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 Tablets, it is best to administer sucralfate 2 hours after the Levofloxacin 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 coadministered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: - Calcium carbonate

Digoxin - Glibenclamide

Ranitidine.

Effect of levofloxacin on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33 % when coadministered 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 the 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, antipsychotic). (See section 4.4 QT interval prolongation).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor. Other forms of interactions

Meals

There is no clinically relevant interaction with food. Levofloxacin Tablets may therefore be administered regardless of food intake.

4.6 Fertility, pregnancy and lactation

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Pregnancy

Clinical data on exposed pregnancies with Esomeprazole Tablets 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 fetal/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Amoxicillin passes the placenta and fetal plasma concentrations are approximately 25-30% of the maternal plasma concentrations.

Data on a limited number of exposed pregnancies indicate no adverse effects of amoxicillin on pregnancy or on the health of the fetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Amoxicillin diffuses into the breast milk (approx. 10% of the corresponding serum concentration) and in rare cases this can lead to diarrhea and/or fungal colonization of the mucosa in the infant. The possibility of sensitization of the infant to beta-lactam drugs should also be considered.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Pregnancy

There are limited amount of data with respect to 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 weightbearing cartilage of the growing organism, levofloxacin must not be used in pregnant women.

Breast-feeding

Levofloxacin tablets are 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 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

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

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

(B) AMOXICILLIN TABLETS USP 1000 MG:

No effects on the ability to drive and to use machines have been observed.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

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).

4.8 Undesirable effects

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Summary of the safety profile

Headache, abdominal pain, diarrhea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency very common >1/10; common >1/100 to <1/10; uncommon >1/1,000 to <1/100; rare >1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

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, fundic gland polyps (benign)
	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)
	Not known	Subacute cutaneous lupus erythematosus (see section 4.4)
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

(B) AMOXICILLIN TABLETS USP 1000 MG:

In this section undesirable effects are defined as follows:
Common: 10%, or less, but greater than 1%
Uncommon: 1%, or less, but greater than 0.1%
Rare: 0.1% or less, but greater than 0.01%
Very rare, including isolated cases: 0.01% or less
Infections and infestations
Uncommon
Prolonged and repeated use of the preparation can result in superinfections and colonization with resistant organisms or yeasts such as oral and vaginal candidiasis.
Blood and the lymphatic system disorders
Rare
Eosinophilia and haemolytic anaemia have been reported rarely.
Very rare
There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia,, myelosuppression, agranulocytosis, prolongation of bleeding time, and prolongation of prothrombin time.
However, these changes were reversible on discontinuation of therapy.
Immune system disorders Rare
Laryngeal oedema, serum sickness, allergic vasculitis and anaphylactic shock may occur in rare cases.
Nervous system disorders
Rare
CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Gastrointestinal disorders:
Common
Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking amoxicillin during meals. If severe and persistent diarrhoea occurs, the very rare possibility of pseudomembranous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.
Rare
A superficial discoloration of the teeth (especially in case of the suspension) is rare. Usually the discoloration can be removed by teeth brushing.
Very rare
Development of a black tongue.
Hepato-biliary disorders:
Uncommon

Moderate and transient increase of liver enzymes. Rare reports of hepatitis and cholestatic jaundice.
Skin and subcutaneous tissue disorders:
Common
Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5 – 11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.
Rare:
Angioneurotic oedema (Quincke's oedema)
Erythema multiforme exudativum
Acute generalized pustulosis
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Bullous and exfoliative dermatitis
Renal disorders Rare:
Acute interstitial nephritis may occur in rare cases. General disorders and administration site conditions Rare:
In rare cases drug fever has been reported.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.
Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Common (≥1/100 to**	**Uncommon (≥1/1,000 to**	**Rare (≥1/10,000 to**	**Not known (cannot be**
	<1/10)	**<1/100)**	**<1/1,000)**	**estimated from available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity	Anaphylactic shock[a] Anaphylactoid shock [a]
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma

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
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion Paraesthesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision	Transient vision loss
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest
				Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged
Vascular disorders			Hypotension	

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 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 Hepatitis
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) 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		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

a Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

b Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include:

• attacks of porphyria in patients with porphyria.

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 the PPB website https://pv.pharmacyboardkenya.org.

4.9 Overdose

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

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 utilized.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Symptoms of overdose:

Amoxicillin is not generally associated with acute toxic effects, even when accidentally consumed in high doses.

Over dosage can lead to symptoms such as gastrointestinal disturbances and fluid and electrolyte imbalance. In patients with severely impaired renal function, large overdoses can result in signs of renal toxicity; Crystalluria is possible

Management of overdose:

There is no specific antidote for an overdose of amoxicillin.

Treatment consists primarily of administration of activated charcoal (a gastric lavage is usually not necessary), or symptomatic measures. Particular attention should be paid to the water and electrolyte balance of the patients.

Amoxicillin can be eliminated via hemodialysis.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of levofloxacin 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.

5.0 Pharmacology

5.1 Pharmacodynamic Properties

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

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.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterized as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomized to receive Esomeprazole Tablets solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral Esomeprazole Tablets for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the Esomeprazole Tablets treated group compared to 10.3% for the placebo group. At 30

days post-treatment, the occurrence of rebleeding in the Esomeprazole Tablets treated versus the placebo treated group 7.7% vs 13.6%.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

Clinical efficacy

In two studies with ranitidine as an active comparator, Esomeprazole Tablets showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, Esomeprazole Tablets showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

(B) AMOXICILLIN TABLETS USP 1000 MG:

ATC-Code: J01CA04

Pharmacotherapeutic group: ß-lactam antibacterial, Penicillin with extended spectrum.

Mode of action

Amoxicillin is an aminobenzyl penicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

PK/PD relationship

For amoxicillin, time above MIC (T>MIC) is the key pharmacodynamic parameter in predicting a successful clinical and bacteriological outcome.

Mechanism of resistance

Bacteria may be resistant to amoxicillin due to production of beta-lactamases which hydrolyse

aminopenicillins, due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to a variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiifectives for systemic use – Antibacterials for systemic use – Quinolone antibasterials – Fluoroquinolones
ATC code: 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(s) of resisance
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 in Pseudomonas aeruginosa) and efflux mechanisms may also 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. Breakpoints
The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).
EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriacae	≤1 mg/L	>2 mg/L
Pseudomonas spp.	≤1 mg/L	>2 mg/L
Acinetobacter spp.	≤1 mg/L	>2 mg/L
Staphylococcus spp.	≤1 mg/L	>2 mg/L
S.pneumoniae [1]	≤2 mg/L	>2 mg/L
Streptococcus A,B,C,G	≤1 mg/L	>2 mg/L
H.influenzae[2, 3] *M.catarrhalis* [3]	≤1 mg/L	>1 mg/L
Non-species related breakpoints [4]	≤1 mg/L	>2 mg/L

1. 1. The breakpoints for levofloxacin relate to high dose therapy.
2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with H. influenzae.
3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

5. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

5.2 Pharmacokinetic properties

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the Risomer 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 metabolizers.

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 b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dosedependent 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.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Absorption:

The absolute bioavailability of amoxicillin depends on the dose and ranges between 75 and 90%. In the dose range between 250 mg and 750 mg the bioavailability (parameters: AUC and/or recovery in urine) is linearly proportional to the dose. At higher doses the extent of absorption decreases. The absorption is not affected by concomitant food intake. Oral administration of a single dose of 500 mg amoxicillin results in plasma concentrations of 6 - 11 mg/l. After administration of a single dose of 3 g amoxicillin, the plasma concentrations reach 27 mg/l. Peak plasma concentrations are present about 1-2 hours after administration.

Distribution:

Protein binding for amoxicillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. In healthy meninges amoxicillin diffuses badly in the liquor cerebrospinal is. In inflamed meninges the concentration can reach approximately 20 % of the concentration in blood. Amoxicillin crosses the placenta and a small percentage is excreted into the breast milk.

Biotransformation and elimination:

The main route of excretion of amoxicillin is the kidney. About 60-80% of an oral dose of amoxicillin are excreted in unchanged active form in the urine within 6 hours of administration, and a small fraction is excreted in the bile. Approximately 7 - 25% of the administered dose is metabolized to inactive penicilloic acid. The serum half-life in patients with normal renal function is approximately 1 – 1,5 hour. In patients with end-stage renal failure the half-life ranges between 5 to 20 hours. The substance is haemodialysable.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

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 500 mg 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 mg dose

Clcr [ml/min]	< 20	20 - 49	50 - 80
ClR [ml/min]	13	26	57
t1/2 [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 small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

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.

(B) AMOXICILLIN TABLETS USP 1000 MG:

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

(C) LEVOFLOXACIN TABLETS USP 500 MG:

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 photocarcinogenity 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

(A) ESOMPERAZOLE MAGNESIUM DELAYED RELEASE TABLETS 40 MG:

Maize starch
Microcrystalline cellulose
Methyl paraben
Propyl paraben
Povidone (PVPK-30)
Isopropyl alcohol*
Sodium starch glycolate
Magnesium stearate
Purified talc
Croscarmellose sodium
Iron oxide red
Precoat 2 enteric coat & Titanium dioxide
Iso Propyl Alcohol
Methylene Di Chloride

(B) AMOXICILLIN TABLETS USP 1000 MG:

Crospovidone
P.V.P.K.30
Isopropyl Alcohol
Magnesium Stearate
Talcum
Film coat FC Titanium Dioxide
Isopropyl Alcohol
Methylene Dichloride
Diethyl Phthalate

(C) LEVOFLOXACIN TABLETS USP 500 MG:

Micro Crystalline Cellulose Phosphate
Aerosil
Sodium Starch Glycolate
Starch
PVP K-30
Purified Water
Magnesium Stearate

Talcum
Cross Carmellose Sodium
Film coat FC titanium dioxide
Colour lake Ponceau-4R
Isopropyl Alcohol
Methylene Dichloride Diethyl phthalate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months from the date of manufacture.

6.4. Special precautions for storage

Store in the original packaging in order to protect from moisture
This medicinal product does not require any special temperature storage conditions

6.5. Nature and contents of container

Alu –Alu blister pack of 1 x 6 tablets, packed in an outer carton along with package insert. Such 7 mono cartons shrink wrapped and packed.

6.6. Special precautions for disposal and other handling

No special requirements

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Saitech Medicare Pvt Ltd, Village Kheri,
Trilokpur Road, Kala Amb-17330, Dist:
Sirmour ,HP, India

Manufacturing site address

Saitech Medicare Pvt Ltd, Village Kheri,
Trilokpur Road, Kala Amb-17330, Dist:
Sirmour ,HP, India

8. Marketing authorization number(s)

H2024/CTD10693/17891

9. Date of first authorization/renewal of the authorization

16-02-2024

10. Date of revision of the text

Nov-2024