

SUMMARY PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LE SURE KIT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated Tablet Contains:

Amoxicillin trihydrate BP

Eq. to Amoxicillin 1000 mg

Excipients q.s.

Colour : Titanium Dioxide

Each Delayed-Release Tablet contains:

Esomeprazole Magnesium USP (as trihydrate)

Eq. to Esomeprazole 40 mg

Excipients Q.S

Colour: Erythrosine & Titanium Dioxide

Each Film coated Tablet Contains:

Levofloxacin hemihydrates USP

Eq. to Levofloxacin 500 mg

Excipients q.s.

Colour : Sunset Yellow & Titanium Dioxide

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Amoxicillin 1000mg -white colored, elongated, biconvex film coated tablets, having break line on one side & plain on the other side.

Esomeprazole 40mg -pink colored round shape enteric coated tablets having break line on one side and plain on the other side.

Levofloxacin 500mg- orange coloured, caplet shaped, film coated tablets. having break line on one side another side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin

Susceptible infections including ear/nose/throat (ENT), genitourinary tract, skin and skin structures, lower respiratory, acute uncomplicated gonorrhea.

Levofloxacin

Levofloxacin 500mg Film-coated 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 500mg Film-coated 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 500mg Film-coated 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.

Esomeprazole

Esomeprazole 40mg tablets are indicated in adults for:

Gastro-oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

Esomeprazole 40mg tablets are indicated in adolescents from the age of 12 years for:

Gastro-oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

4.2 Posology and Method of Administration :

Posology

Amoxicillin

Adult :

>40kg: ENT: mild/moderate: 500mg every 12hrs; severe: 875mg every 12hrs. Lower respiratory tract: 875mg every 12hrs. Skin/skin structure: mild/moderate: 500mg every 12hrs; severe: 875mg every 12hrs. Genitourinary tract: mild/moderate: 500mg every 12hrs; severe: 875mg every 12hrs. Gonorrhoea, acute uncomplicated ano-genital and urethral infections: 3g as single oral dose.

Children

≤3 months: max 30mg/kg per day in 2 divided doses every 12hrs. >3 months (<40kg): ENT, genitourinary, skin: 25mg/kg/day in divided doses every 12hrs. Severe infections, or lower respiratory infections: 45mg/kg/day in divided doses every 12hrs. Gonorrhea: <2yrs: not recommended; prepubertal: amoxicillin 50mg/kg + probenecid 25mg/kg as a single dose.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Method of administration

Tablets are for oral use.

Levofloxacin

Levofloxacin 500mg Film-coated Tablets are administered once or twice daily.

The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.

Levofloxacin 500mg Film-coated Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin; given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology

The following dose recommendations can be given for Levofloxacin 500mg Film-coated Tablets.

Impaired liver function

No adjustment of dose 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 dose is required in the elderly, other than that imposed by consideration of renal function .

Paediatric population

Levofloxacin 500mg Film-coated Tablets is contraindicated in children and growing adolescents

Method of administration

Tablets are for oral use.

Esomeprazole

Posology

Adults

Gastro-oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

40 mg esomeprazole once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.

40mg esomeprazole once daily for 4 weeks after i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is 40 mg esomeprazole 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.

Patients with impaired renal function

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

Patients with impaired hepatic function

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded (see section 5.2).

Elderly

Dose adjustment is not required in the elderly.

Paediatric population

Adolescents from the age of 12 years

Gastro-oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

40 mg esomeprazole once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Children below the age of 12 years

Esomeprazole should not be used in children younger than 12 years since no data is available.

Method of administration

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

For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested. For preparation and administration instructions

4.3 Contraindication :

Amoxicillin

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

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

History of jaundice/hepatic impairment due to amoxicillin.

Levofloxacin

Levofloxacin tablets must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or 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.

Esomeprazole

Hypersensitivity to the active substance esomeprazole, to substituted benzimidazoles or to any of the excipients listed in section 6.1.

Esomeprazole should not be used concomitantly with nelfinavir

4.4 Special warnings and precautions for use

Amoxicillin

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

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

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

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

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

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

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

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

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

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible.

Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

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

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

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

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

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

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin should be interpreted cautiously and confirmed by other diagnostic methods.

Levofloxacin

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. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon .

Clostridium difficile-associated disease

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

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substance that lower the cerebral seizure threshold, such as theophylline. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency

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

Patients with renal impairment

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

Hypersensitivity reactions

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

Esomeprazole

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 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* (see section 5.1).

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 sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors

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 400mg with 100mg of ritonavir; esomeprazole 20mg 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 (see section 4.5).

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 five 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.

4.5 Interaction with other medicinal products and other forms of interactions

Oral anticoagulants :

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on

acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

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

Probenecid

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

4.6 Used in Pregnancy and Lactation

Amoxicillin

Pregnancy :

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

Lactation :

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

Levofloxacin

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. 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.

Lactation :

Levofloxacin 250mg Film-coated Tablets is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be in breast-feeding women.

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. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breastfeeding

It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Therefore Esomeprazole should not be used during breast-feeding.

4.7 Effects on ability to drive and operate machines

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

4.8 Undesirable Effects

Amoxicillin

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

<u>Infections and infestations</u>	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
<u>Blood and lymphatic system disorders</u>	
Reversible leucopenia (including neutropenia)	Rare

Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time ¹	Not known
<u>Immune system disorders</u>	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
<u>Nervous system disorders</u>	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions	Not known
<u>Gastrointestinal disorders</u>	
Diarrhoea	Very common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
<u>Hepatobiliary disorders</u>	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
<u>Skin and subcutaneous tissue disorders</u>	
Skin rash	Uncommon

Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
<u>Renal and urinary disorders</u>	
Interstitial nephritis	Not known
Crystalluria	Not known

Levofloxacin

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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

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 ($\geq 1 / 100$ to $< 1/10$)	Uncommon ($\geq 1 / 1,000$ to $< 1/100$)	Rare ($\geq 1 / 10,000$ to $< 1/1,000$)	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia

Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	Anaphylactic shock ^a Anaphylactoid shock ^a (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	

Esomeprazole

Summary of the safety profile

Headache, abdominal pain, diarrhoea 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 $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1,000$ to

<1/100; rare $\geq 1/10,000$ 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 pre-existing 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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Amoxicillin

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.

Treatment of intoxication

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

Levofloxacin

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

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 utilized.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Amoxicillin

Pharmacotherapeutic group : beta-lactamase inhibitors (beta-lactam antibiotic)

ATC code: J01CR02.

Mode of action

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

PK/PD relationship

The time above the minimum inhibitory concentration ($T > MIC$) is considered to be the major determinant of efficacy for amoxicillin

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Levofloxacin

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones,

ATC code: J01MA12

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

Mode 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 (C_{max}) 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 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.

Esomeprazole

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitor, 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.

5.2 Pharmacokinetic Properties :

Absorption :

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

Distribution :

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial

and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

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

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation :

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination :

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Co-Amoxiclav 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal

impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Levofloxacin

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak

plasma concentrations being obtained within 1h. The absolute bioavailability is approximately

100%. Food has little effect on the absorption of levofloxacin.

Distribution:

Approximately 30 – 40% of levofloxacin is bound to serum protein. 500 mg once daily

multiple dosing with levofloxacin showed negligible accumulation. There is modest but

predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is

achieved within 3 days.

Elimination:

Following oral and intravenous administration of levofloxacin, it is eliminated relatively

slowly from the plasma ($t_{1/2}$: 6 – 8 h). Excretion is primarily by the renal route (>85% of the

administered dose. There are no major differences in the pharmacokinetics of levofloxacin

following intravenous and oral administration, suggesting that the oral and intravenous routes

are interchangeable.

Patients 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:

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 a small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

Esomeprazole

Absorption

Esomeprazole is acid labile and is administered orally as gastro-resistant 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.

5.3 Pre-clinical safety data :

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Amoxicillin

Microcrystalline cellulose
P.V.P K-30
Sodium Starch Glycolate
Colloidal silicon dioxide
Magnesium Stearate
Purified Talc
Isopropyl Alcohol
Methylene Chloride
Titanium dioxide
HPMC
Talcum

Levofloxacin

Maize Starch
Microcrystalline cellulose
Maize Starch
P.V.P K-30
Purified water
Purified Talc
Magnesium Stearate
Sodium Starch Glycolate
Colloidal Anhydrous Silica

Esomeprazole

Mannitol

Sodium Bicarbonate
Povidone K -30
Iso -propyl alcohol
Purified Talc
Magnesium Stearate
Colloidal Anhydrous silica
Crosscarmellose sodium
Elegance ELE 1002 Pink
Iso -propyl alcohol
Methylene Dichloride
Elegance ELW1001- White Precoat

6.2 Incompatibilities :

Not applicable.

6.3 Shelf – Life :

36 months.

6.4 Special Precaution for Storage :

Store at temperature not exceeding 25°C. Keep out of reach of children.

6.5 Nature and Content of Containers :

3 Tablets pack in one Alu -Alu blister

6.6 Special Precautions for Disposal and other handling :

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Manufacturer:

Brussels Laboratories Pvt. Ltd.
33, Changodar industrial Estate,
Changodar – 382 210
Ahmedabad (Gujarat) India.

Marketing Authorisation Holder:

National Pharmacy ltd
P.O Box 17843-00500 Nairobi, Kenya. Colchester Park, Off Mombasa Road

8. MARKETING AUTHORISATION NUMBER

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10. DATE OF REVISION OF THE TEXT

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