**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product:

PYLOBACT NEO 2

## 2. Qualitative and quantitative composition

**Amoxicillin Tablets**
Each film-coated tablet contains: Amoxicillin Trihydrate equivalent to Amoxicillin 1000 mg
**Levofloxacin Tablets**
Each film-coated tablet contains: Levofloxacin hemihydrate equivalent to Levofloxacin 500 mg
**Esomeprazole**
Each Gastro-resistant Tablet contains: Esomeprazole Magnesium (amorphous) equivalent to Esomeprazole 20 mg.
For the full list of excipients, see section 6.1

## 3. Pharmaceutical form

**Amoxicillin 1000 mg tablet:** Orange coloured capsule shaped, biconvex film coated tablets.

**Esomeprazole 20 mg tablet:** Light brick red to brown coloured, oval, biconvex, film coated tablets with 'E5' debossed on one side and plain on other side.

**Levofloxacin 500 mg tablet:** Light yellowish to pink coloured, film coated, biconvex oval shaped debossed with '500' on one side

## 4. Clinical particulars

### 4.1 Therapeutic indications

PYLOBACT NEO 2 is indicated in the eradication of H. pylori in active chronic gastritis, duodenal and gastric ulcers.

### 4.2 Posology and method of administration

PYLOBACT NEO 2 contains 7 kits to be taken in 7 days.
Each one-day kit contains: Two Amoxicillin 1000 mg film coated Tablets, Two Levofloxacin 500 mg film coated Tablets and Two Esomeprazole 20 mg Gastro-resistant Tablets.
One tablet of amoxicillin 1000mg, one tablet of levofloxacin 500mg and one tablet of esomeprazole 20mg should be taken every morning and a repeat of the same every evening for the duration of therapy.
The recommended therapy is for seven days and may be extended as per the Physicians advice.

Esomeprazole gastro-resistant tablets, levofloxacin and amoxicillin tablets should not be crushed or chewed, and should be swallowed whole. In case wherein the dose modification of any individual component is required, PYLOBACT NEO 2 containing levofloxacin 500 mg, esomeprazole gastro-resistant 20 mg, amoxicillin 1000 mg tablets should not be used.

**Special Populations**

Paediatric Use

PYLOBACT NEO 2 of esomeprazole, levofloxacin or amoxicillin is contraindicated in paediatric patients.

Geriatric Use

No adjustment of dosage is required in the elderly.

Renal Impairment

It is recommended to avoid the use of PYLOBACT NEO 2 of esomeprazole, levofloxacin or amoxicillin, in patients with renal impairment.

Hepatic Impairment

It is recommended to avoid the use of PYLOBACT NEO 2 of esomeprazole, levofloxacin or amoxicillin, in patients with hepatic impairment.

**Method of administration**

For oral use. Esomeprazole gastro-resistant tablets, levofloxacin film-coated tablets and amoxicillin film-coated tablets should not be crushed or chewed, and should be swallowed whole.

## 4.3 Contraindications

1. A history of allergic reaction to any of the penicillins and infections caused by penicillinase producing organism are contraindicated.
2. Levofloxacin tablets must not be used:
    - in patients hypersensitive to levofloxacin, or other quinolones or any of the excipients listed in section 6.1
    - in patients with epilepsy,
    - in patients with history of tendon disorders related to fluoroquinolone administration,
    - in children or growing adolescents,
    - during pregnancy,
    - in breast-feeding women.
3. Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed in section 6.1.

Esomeprazole should not be used concomitantly with nelfinavir and atazanavir.

## 4.4 Special warnings and precautions for use

Before initiating therapy with NEXILEV KIT, carefully inquire from the patient concerning hypersensitivity to penicillinS cephalosporin and other allergens. Serious and occasionally fatal hypersensitivity reactions (anaphylactic) have been reported in patients on penicillin therapy.

When prescribing Esomeprazole for eradication of Helicobacter pylori, possible drug interactions for all components in the triple therapy should be considered. Caution should be taken when using fluroquinolones, including levofloxacin, in patients with known risk
factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III
antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction,bradycardia)
Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations

**Esomeprazole**
Gastrointestinal infections
Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.
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.

**Levofloxacin**
The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products.
Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may reported as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. The daily dose should be adjusted in elderly patients based on creatinine clearance (see section 4.2). At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s)

should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.
Clostridium difficile-associated disease (CDAD)
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of CDAD. CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis.
Patients predisposed to seizures
Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy
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. PYLOBACT NEO 2 is not recommended for use in patients requiring any kind of dose adjustment

**Amoxicillin**
Hypersensitivity reactions
Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.
Convulsions
Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors
Renal impairment
In patients with renal impairment, the dose should be adjusted according to the degree of impairment. PYLOBACT NEO 2 is not recommended for use in patients requiring any kind of dose adjustment.
Skin reactions
The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis. This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.
Crystalluria In patients with reduced urine output, crystalluria has been reported 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

## 4.5 Interaction with other medicinal products and other forms of interaction

**Effects of Esomeprazole on the pharmacokinetics of other drugs**

*Protease inhibitors*
Esomeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported

interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.
For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended.
*Methotrexate*
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of Esomeprazole may need to be considered.
*Tacrolimus*
Concomitant administration of Esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.
*Medicinal products with pH dependent absorption*
Gastric acid suppression during treatment with Esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with Esomeprazole.
*Medicinal products metabolised by CYP2C19*
Esomeprazole inhibits CYP2C19, the major Esomeprazole-metabolising enzyme. Thus, when Esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing Esomeprazole for on-demand therapy.
*Diazepam*
Concomitant administration of 30 mg Esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.
*Phenytoin*
Concomitant administration of 40 mg Esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with Esomeprazole is introduced or withdrawn.
*Warfarin*
Concomitant administration of 40 mg Esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant Esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

**Levofloxacin**

Iron salts, zinc salts, magnesium- or aluminium-containing antacid, didanosines

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with Levofloxacin tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after Levofloxacin tablet administration (see section 4.2). Calcium salts have a minimal effect on the oral absorption of levofloxacin.

*Sucralfate*

The bioavailability of Levofloxacin tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration (see section 4.2).

*Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs*

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study.

However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

*Probenecid and cimetidine*

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

**Amoxicillin:**

1. Allopurinol may increase possibilities of hypersensitivity reactions.
2. Chloramphenicol, tetracyclines, Sulphonamides and macrolide antibiotics may interfere with bactericidal effects of penicillins.
3. Oral contraceptives may be less effective and increase break through bleeding may occur.
4. Probenecid may decrease renal tubular secretion of Amoxicillin resulting in its increased blood levels and or Amoxicillin toxicity.

## 4.6 Fertility, Pregnancy and Lactation

**Amoxicillin**

Use in pregnancy:

Animal studies with Amoxicillin have shown no teratogenic effects. The product has been in extensive clinical use since 1972 and its suitability in human pregnancy has been well documented in clinical studies. When antibiotic therapy is required during pregnancy, Amoxicillin may be considered appropriate when the potential benefits outweigh the potential risks associated with treatment.

Use in lactation:

Amoxicillin may be given during lactation. With the exception of the risk of sensitization associated with the excretion of trace quantities of amoxicillin in breast milk, there are no known detrimental effects for the breast-fed infant.

**Esomeprazole**

Pregnancy

Clinical data on exposed pregnancies with Esomeprazole are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with Esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of Esomeprazole.

Breast-feeding

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

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

**Levofloxacin**

Pregnancy

There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However, in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the

growing organism, levofloxacin must not be used in pregnant women (see section 4.2 and 5.3).

Breast-feeding
The product is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to the experimental data suggests risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

Fertility
Levofloxacin caused no impairment of fertility or reproductive performance.

## 4.7 Effects on ability to drive and use machines

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

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

**Amoxicillin**
Adverse effects on the ability to drive or operate machinery have not been observed

## 4.8 Undesirable effects

**Esomeprazole**

| System Organ Class | Frequency | Undesirable Effect |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Leukopenia, thrombocytopenia |
| | Very rare | Agranulocytosis, pancytopenia |
| Immune system disorders | Rare | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock |
| Metabolism and nutrition disorders | | Uncommon Peripheral oedema |
| | Rare | Hyponatraemia |
| | Not known | • Hypomagnesaemia (see section 4.4); severe hypomagnesaemia can |

| | | |
|---|---|---|
| | | correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia. |
| Psychiatric disorders | Uncommon | Insomnia |
| | Rare | Agitation, confusion, depression |
| | Very rare | Aggression, hallucinations |
| Nervous system disorders | Common | Headache |
| | Uncommon | Dizziness, paraesthesia, somnolence |
| | Rare | Taste disturbance |
| Eye disorders | Rare | Blurred vision |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Respiratory, thoracic and mediastinal disorders | Rare | Bronchospasm |
| Gastrointestinal disorders | Common | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting |
| | Uncommon Dry mouth | |
| | Rare | Stomatitis, gastrointestinal candidiasis |
| | Not known | Microscopic colitis |
| Hepatobiliary disorders | Uncommon | Increased liver enzymes |
| | Rare | Hepatitis with or without jaundice |
| | Very rare | Hepatic failure, encephalopathy in patients with preexisting liver disease |
| Skin and subcutaneous tissue disorders | Uncommon | Dermatitis, pruritus, rash, urticaria |
| | Rare | Alopecia, photosensitivity |
| | Very rare | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) |
| Musculoskeletal and connective tissue disorders | | Uncommon Fracture of the hip, wrist or spine (see section 4.4) |
| | Rare | Arthralgia, myalgia |
| | Very rare | Muscular weakness |
| Renal and urinary disorders | Very rare | Interstitial nephritis; in some patients renal failure has been reported concomitantly. |
| Reproductive system and breast disorders | Very rare | Gynaecomastia |
| General disorders and administration site conditions | Rare | Malaise, increased sweating |

**Levofloxacin**

| **System organ class** | **Common 21/100 to < 1/10)** | **21/1,000 to <1/100)** | **Rare 21/10,000 to < 1/1,000)** | **Not known (cannot be estimated from available data)** |
|---|---|---|---|---|
| Infections and infestations | | Fungal infection including Candidia infection Pathogen resistance | | Genital moniliasis |
| Reproductive System | | | | Vaginitis |
| Blood and lymphatic system disorders | | Leukopenia Eosinophilia | Thrombocytopenia Pancytopenia Neutropenia | Agranulocytosis Haemolytic anaemia |
| Immune system disorders | | | Angioedma Hypersensitivity (see section 4.4) | Anaphylactic shock? Anaphylactoid shock (see section 4.4) |
| Metabolism and nutrition disorders | | Anorexia | Hypoglycaemia particularly in diabetic patients (see section 4.4) | Hyperglycaemia Hypoglycaemic coma (see section 4.4) |
| Psychiatric disorders | Insomnia | Anxiety Confusional state Nervousness | Psychotic reaction (with e.g. hallucinations, paranoia) Depression Agitation Abnormal dreams Nightmares | Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4) |
| Nervous system disorders | Headache Dizziness | Somnolence Tremor Dysgeusia | Convulsions (see section 4.3 and 4.4) neuropathy (see Parasethesia | Peripheral sensory section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including |
| | | | | anosmia Dyskinesia Extrapyramidal disorder |

| | | | | |
|---|---|---|---|---|
| | | | | Ageusia<br>Synocope<br>Benign intracranial hypertension<br>Hypoaesthesia |
| Eye disorders | | | Visual disturbances<br>Transient vision such as blurred vision (see section 4.4) | loss (see section 4.4) |
| Ear and Labyrinth disorders | | Vertigo | Tinnitus | Hearing loss<br>Hearing impaired |
| Cardiac disorders | | | Tachycardia<br>Palpitation | Ventricular tachycardia, which may result in cardiac arrest<br>Venticular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9) |
| Vascular disorders | Applies to i.v. form only:<br>Phlebitis | | Hypotension | |
| Respiratory, thoracic and medistinal | | Dyspnoea | | Bronchospasm<br>Pneumonitis |
| disorders | | | | allergic |
| Gastro-intestinal disorders | Diarrhoea<br>Vomiting<br>Nausea | Abdominal pain<br>Dyspepsia<br>Flatulence<br>Constipation | | Diarrhoea - haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis |

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| | | | | (see section 4.4)<br>Pancreatitis |
| Hepatobiliary disorders | Hepatic enzyme increased (ALT/AST, alkaline phosphatase, CGT) | Blood bilirubin increased | | Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily with severe underlying diseases (see section 4.4)<br>Hepatitis |
| Skin and subcutaneous tissue disorders | | Rash<br>Pruritus<br>Urticaria<br>Hyperhidrosis | | Toxic epidermal necrolysis<br>Stevens-Johnson syndrome<br>Erythema multiforme<br>Photosensitivity reaction (see section 4.4)<br>Leukocytoclastic vasculitis<br>Stomatitis |
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia | Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) | Rhabdomyolysis<br>Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and |
| | | | Muscle weakness which may be of special importance in patients with myasthenia gravis (see section 4.4) | 4.4)<br>Ligament rupture<br>Muscle rupture<br>Arthritis |
| Renal and Urinary disorders | | Blood creatinine increased | Renal failure acute (e.g. due to interstitial nephritis) | |
| General disorders and administration site conditions | Applies to i.v. form Asthenia only:<br>Infusion site reaction | | Pyrexia | Pain (including pain in back, chest, and extremities) |

| | | | | |
|---|---|---|---|---|
| | (pain, reddening) | | | |

**Amoxicillin**
As with other penicillin, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillin and in those with a history of allergy, asthma, hay fever or uetica. The following adverse reactions have been reported as associated with the use of penicillin.

*Gastrointestinal:* Glossitis, stomatits, nausea, vomiting, diarrhea, entero-colis and pseudomembranous colitis. These reactions are usually associated with oral dosage forms of the drug.
*Hypersensitivity*: Occurrence of an erythematous, midly pruritic; maculopapular skin rash has been reported.

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

## 4.9 Overdose

**Esomeprazole**
There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg Esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

**Levofloxacin**
According to toxicity studies in animals or clinical pharmacology studies performed with supra- therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin tablets are central nervous symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.
CNS effects include confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.

No specific antidote exists.

**Amoxicillin**
Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water/electrolyte balance. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.
Amoxicillin may be removed from the circulation by haemodialysis.

## 5. Pharmacological properties
## 5.1 Pharmacodynamic properties
## 5.2 Pharmacodynamic properties

**Esomeprazole**
Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors

ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar Pharmacodynamic activity.

Mechanism of action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+ -ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects
After oral dosing with Esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg Esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6–7 hours after dosing on day five.
After five days of oral dosing with 20 mg and 40 mg of Esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for Esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for Esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown. Healing of reflux esophagitis with Esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.
One week treatment with Esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of H. pylori in approximately 90% of patients.
After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

**Levofloxacin**
Pharmacotherapeutic group:
ATC code: Quinolone antibacterials - Fluoroquinolones
J01MA12
Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin.

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

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

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

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

**Amoxicillin**
Mechanisms of Action/Effect
Amoxicillin is similar to penicillin in its bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.
Amoxicillin is bactericidal. Like all penicillins it acts by interfering with the synthesis of the cell wall of the bacterium.

Amoxicillin is inactivated by penicillinase. Penicillinase-producing strains of Staphylococcus aureus and Gram-negative organisms (e.g. Escherichia coli, Proteus, Klebsiella) are resistant.

Complete cross-resistance occurs with ampicillin and amoxicillin.

## 5.3 Pharmacokinetic properties

**Esomeprazole**

Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of Esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. For 20 mg Esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of Esomeprazole although this has no significant influence on the effect of Esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of Esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of Esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of Esomeprazole sulphone, the main metabolite in plasma.

Elimination

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration.

The plasma elimination half-life is about 1.3 hours after repeated once daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of Esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of Esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Linearity/non-linearity

The pharmacokinetics of Esomeprazole has been studied in doses up to 40 mg twice daily The area under the plasma concentration-time curve increases with repeated administration of Esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by Esomeprazole and/or its sulphone metabolite.

**Special patient populations**

*Poor metabolisers*

Approximately 2.9 ±1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of Esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg Esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of Esomeprazole.

*Gender*

Following a single dose of 40 mg Esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. These findings have no implications for the posology of Esomeprazole.

*Hepatic impairment*

The metabolism of Esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of Esomeprazole. Therefore, a maximum

of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

*Renal impairment*

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of Esomeprazole but not for the elimination of the parent compound, the metabolism of Esomeprazole is not expected to be changed in patients with impaired renal function.

*Older people*

The metabolism of Esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

*Paediatric population*

Adolescents 12-18 years:

Following repeated dose administration of 20 mg and 40 mg Esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (tmax) in 12- to 18-year-olds was similar to that in adults for both Esomeprazole doses.

**Levofloxacin**

Absorption

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

Food has little effect on the absorption of levofloxacin.

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

regimen.

Distribution

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

Penetration into tissues and body fluids:

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

Biotransformation

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

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 – 8 h). Excretion is primarily by the renal route (>85% of the administered dose).

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

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

Linearity

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

Special populations

Subjects with renal insufficiency

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

Pharmacokinetics in renal insufficiency following single oral 500 m dose

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

Elderly subjects

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

Gender differences

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

**Amoxicillin**

Amoxicillin is stable in the acid gastric secretion and is rapidly absorbed from the gastrointestinal tract after oral administration. The presence of food does not interfere with this process. Peak plasma concentrations are obtained in about two hours, producing around 2.5 times the peak concentration resulting from comparable doses of ampicillin.

Protein binding is similar to that of ampicillin: up to 25%.
Effective levels in the cerebrospinal fluid are obtained only in the presence of inflammation and then irregularly. About 60% of an orally administered dose is excreted unchanged in the urine. It penetrates
well in to purulent and mucoid sputum.

In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inuline clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally

## 5.4 Preclinical safety data

**Esomeprazole**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

Non-clinical data reveal no special hazard based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

**Levofloxacin**

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses.

Levofloxacin did not show any genotoxic potential in a photo mutagenicity assay, and it reduced tumour development in a photo carcinogenicity study.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

## 6. Pharmaceutical Particulars

### 6.1 List of Excipients

**Levofloxacin 500 mg Film-coated Tablets:**

Microcrystalline cellulose
Hypermellose,
Polysorbate 80,
Purified water
Crospovidone
Magnesium stearate
Opadry yellow

**Amoxicillin 1000 mg Film-coated Tablets:**

Microcrystalline cellulose
Sodium starch glycollate
Colloidal anhydrous silica
Purified talc
Magnesium stearate
Hypromellose
Titanium dioxide
Masking flavour Permaseal
Lake of sunset yellow
Polyethylene glycol 400
Purified water

**Esomeprazole 20 mg Gastro-resistant Tablets:**
Hydroxypropyl cellulose
Crospovidone
Purified water
PovidonE
Macrogel 400
Purified Talc
Isopropyl alcohol
Hypromellose phthalate (HP-55S and HP-50)
Diethylphthalate
Acetone
Macrogel 6000
Methylene chloride.

**6.2 Incompatibilities**
Not Applicable

**6.3 Shelf-Life**
24 Months

**6.4 Special Precautions for storage**
Store below 30℃
Protect from moisture.

**6.5 Nature and Content of container**
Alu – Alu Blister Pack
2 levofloxacin 500 mg Tablets
2 amoxicillin 1000 mg Tablets
2 esomeprazole 20 mg Tablets

In a unit box Pack size: 6x7s

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

**7. Marketing Authorization Holder**

SUN PHARMACEUTICAL INDUSTRIES LIMITED

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E-Mail: anurag.agrawal@sunpharma.com

**8. Marketing Authorization Number**
CTD9756

**9. Date of first authorization/renewal of the authorization**
29/06/2023

**10. Date of revision of the text**
05/05/2025