SUMMARY OF PRODUCT CHARACTERISTICS

PYLOBACT NEO 2
(Combikit of Amoxicillin Tablets 1000 mg + Levofloxacin Tablets 500 mg + Esomeprazole 20 mg Gastro-resistant Tablets)

1. NAME OF THE MEDICINAL PRODUCT
PYLOBACT NEO 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
PYLOBACT NEO 2, Each Combikit contains:

Two Amoxicillin Tablets 1000 mg
Two Levofloxacin Tablets 500 mg
Two Esomeprazole Gastro-resistant Tablets 20 mg

Amoxicillin Tablets 1000 mg
Each film-coated tablet contains:
Amoxicillin Trihydrate equivalent to Amoxicillin ……..……..1000 mg

Levofloxacin Tablets 500 mg
Each film-coated tablet contains:
Levofloxacin hemihydrate equivalent to Levothyroxin ……..….500 mg

Esomeprazole Gastro-resistant Tablets 20 mg
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
Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications [1,2,3]
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **PYLOBACT NEO 2** and other antibacterial drugs, this **PYLOBACT NEO 2** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of

therapy.

Levofloxacin tablets, esomeprazole gastro-resistant tablets and amoxicillin tablets taken together are indicated as a second line treatment of eradication of *Helicobacter pylori* infection, and duodenal ulcer disease to eradicate *Helicobacter pylori*, after failure of triple therapy with proton pump inhibitor plus clarithromycin plus amoxicillin.

In patients who fail therapy with this **PYLOBACT NEO 2**, perform susceptibility testing. If resistance to levofloxacin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

4.2 Posology and method of administration [1,2]

The recommended adult oral dosage is one tablet of levofloxacin 500 mg plus one tablet of esomeprazole gastro-resistant 20 mg plus one tablet of amoxicillin 1000 mg, each taken twice daily, for 14 days. Inform patients that 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

Pediatric Use

PYLOBACT NEO 2 of esomeprazole, levofloxacin or amoxicillin is contraindicated in pediatric 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 [4,5,6]

PYLOBACT NEO 2 is contraindicated in:

- In patients with a history of immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam), to esomeprazole or levofloxacin or any fluoroquinolone antibiotic, or any penicillin or any of the excipients of the formulation
- In patients taking nelfinavir
- In patients with epilepsy
- In patients with history of tendon disorders related to fluoroquinolone administration
- In children or growing adolescents
- During pregnancy
- In breast-feeding women

4.4 Special warnings and precautions for use [4,5,6]

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** and **5.2**).

Absorption of vitamin B_{12}
Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypoor achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

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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. Reported 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 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is reported 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)**.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section **5.1** and **5.2**). 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.

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 (see section **4.8**). Treatment of these patients with Levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see section **4.3**).

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic

dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

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

Levofloxacin may be used in the treatment of acute bacterial sinusitis and acute exacerbation of chronic bronchitis when these infections have been adequately diagnosed.

Resistance to fluoroquinolones of *E. coli*: The most common pathogen involved in urinary tract infections varies across geographies. 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 reported *in vitro Bacillus anthracis* susceptibility data and on animal experimental data together with limited reported human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

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 (see section **4.8**). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin tablets should be stopped immediately and appropriate treatment initiated without delay (e.g. oral metronidazole or vancomycin). Medicinal products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures
Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy (see section **4.3**) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline (see section **4.5**). In case of convulsive seizures (see section **4.8**), treatment with levofloxacin should be discontinued.

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

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin tablets should be adjusted in patients with renal impairment. **PYLOBACT NEO 2** is not recommended for use in patients requiring any kind of dose adjustment (see section **4.2**).

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

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section **4.8**). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section **4.8**).

Prevention of photosensitisation
Photosensitisation has been reported with levofloxacin (see section **4.8**). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section **4.5**).

Psychotic reactions
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour- sometimes after only a single dose of levofloxacin (see section **4.5**). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

QT interval prolongation
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

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

(see section **4.2, 4.5**, **4.8** and **4.9**).

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones.

Patients under treatment with levofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section **4.8**).

Hepatobiliary disorders
Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section **4.8**). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

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

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section **4.8**).

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

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

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 (see section **4.3** and **4.8**). Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse 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.

Non-susceptible microorganisms
Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin (see section **5.1** and **5.2**). This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Convulsions
Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders (see section **4.8**).

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 (see section **4.2**).

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 (AGEP, see section **4.8**). This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.

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.

Jarisch-Herxheimer reaction
The Jarisch-Herxheimer reaction has been reported following amoxicillin treatment of Lyme disease (see section **4.8**). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms
Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section **4.8**). 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 consulted and an appropriate therapy initiated. Antiperistaltic medicinal products are contra-indicated in this situation.

Prolonged therapy
Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported (see section **4.8**).

Anticoagulants
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 (see section **4.5** and **4.8**).

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 (see section **4.8** and **4.9**).

Interference with diagnostic tests
Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

4.5 Interaction with other medicinal products and other forms of interaction [4,5,6]

Esomeprazole
Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not reported. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers reported a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers reported a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without

omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36-39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section **4.4**) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section **4.3**).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect reported on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In 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. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects reportedly increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products 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 reported a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin
Concomitant administration of 40 mg esomeprazole reported a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole
Omeprazole (40 mg once daily) have been reported to increase voriconazole (a CYP2C19 substrate) C_{max} and AUCτ by 15% and 41%, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over stud reportedly increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride
In healthy volunteers, concomitant administration of 40 mg esomeprazole reported a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval reported after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see section **4.4**).

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial reported that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and

ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel
Results from studies in healthy subjects have reported a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o.daily) reported decreased exposure to the active metabolite of clopidogrel by an average of 40% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

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

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

Investigated medicinal products with no clinically relevant interaction

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

Naproxen or rofecoxib
Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not report any clinically relevant pharmacokinetic interactions during short-term studies
Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), reported a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole is not regularly required

in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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

Paediatric population
Interaction studies have only been reported in adults. The **PYLOBACT NEO 2** is not recommended for use in pediatric patients.

Levofloxacin
Effect of other medicinal products on levofloxacin

Iron salts, zinc-salts, magnesium- or aluminium-containing antacids, didanosine

Levofloxacin absorption is reported to be significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine *(only didanosine formulations with aluminium or magnesium containing buffering agents)* are administered concomitantly with levofloxacin tablets.. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cautions such as iron salts, zinc-salts or magnesium- or aluminium-containing antacids, or didanosine *(only didanosine formulations with aluminium or magnesium containing buffering agents* should not be taken 2 hours before or after Levofloxacin 500mg Film-coated Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate
It has been reported that the bioavailability of levofloxacin 500mg film-coated tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin 500mg film-coated tablets administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were reported with theophylline. 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 reported 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 reported to be 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 renally impaired patients.

Other relevant information
Clinical pharmacology studies have reported that the pharmacokinetics of levofloxacin was not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of levofloxacin on other medicinal products

Ciclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section **4.4**).

Drugs known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides and, antipsychotics) (see section **4.4**)

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

Other forms of interactions

Food

There is no clinically relevant interaction reported with food. Levofloxacin 500mg film-coated tablets may therefore be administered regardless of food intake.

Amoxicillin

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.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio reported 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 (see section **4.4** and **4.8**).

Methotrexate

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

4.6 Pregnancy and lactation 4[5,6]

Pregnancy

There are no adequate and well controlled studies of kit containing esomeprazole, levofloxacin or amoxicillin (used separately or together) reported in pregnant women. **PYLOBACT NEO 2** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and there is no appropriate alternative therapy (see section **4.4**).

Information reported on use of each component of the **PYLOBACT NEO 2** during pregnancy is provided below.

Esomeprazole

Reported clinical data on exposed pregnancies with esomeprazole are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies reported from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not report direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not repot 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 reported on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole. Animal studies do not report direct or indirect harmful effects with respect to reproductive toxicity.

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

Levofloxacin

There are limited amount of data reported with respect to the use of levofloxacin in pregnant women. Animal studies do not report direct or indirect harmful effects with respect to reproductive toxicity (see section **4.3**). 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 **4.3** and **5.3**).

Amoxicillin

Animal studies do not report direct or indirect harmful effects with respect to reproductive toxicity. Limited data reported on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Esomeprazole

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

Levofloxacin

Levofloxacin tablets are contraindicated in breast-feeding women. There is insufficient information reported on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of reported human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see section **4.3** and **5.3**).

Amoxicillin

Amoxicillin has been reported to be excreted into breast milk in small quantities with the possible risk of sensitisation. 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.

Fertility

Esomeprazole

It has been reported in animal studies with the racemic mixture that omeprazole given by oral administration do not effects with respect to fertility.

Levofloxacin

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

Amoxicillin

There are no data reported on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have reported no effects on fertility.

4.7 Effects on ability to drive and use machines [4,5,6]

Patients should be advised to be careful while taking this **PYLOBACT NEO 2**. The following effects have been reported with individual component of the **PYLOBACT NEO 2.**

Esomeprazole: Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported (see section **4.8**). 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: No studies on the effects on the ability to drive and use machines have been reported. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section **4.8**).

4.8 Undesirable effects [4,5,6]

Summary of the safety profile of individual component is provided below.

Frequencies are defined using the following convention:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Esomeprazole

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 reported.

Tabulated list of adverse reactions

The following adverse drug reactions have been reported or suspected in the clinical trials programme for esomeprazole and reported post-marketing. None was reported to be dose-related.

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

Levofloxacin

The information given below is based on data reported from clinical studies and on extensive post marketing experience.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (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**)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see section **4.3** and **4.4**) Paraesthesia	Peripheral sensory neuropathy (see section **4.4**) Peripheral sensory motor neuropathy (see section **4.4**) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope

				Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision (see section **4.4**)	Transient vision loss (see section **4.4**)
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see section **4.4** and **4.9**)
Vascular disorders	*Applies to iv form only:* Phlebitis		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (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
Skin and subcutaneous tissue disorders b		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section **4.4**) Leukocytoclastic vasculitis

				Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders (see section **4.3** and **4.4**) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section **4.4**)	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see section **4.3** and **4.4**) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions	*Applies to iv form only:* Infusion site reaction (pain, reddening)	Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

[a]Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
[b]Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been reported with fluoroquinolone administration include: - attacks of porphyria in patients with porphyria

Amoxicillin

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash. The ADRs reported from clinical studies and post-marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.

Infections and infestations	
Very rare	Mucocutaneous candidiasis
Blood and lymphatic system disorders	

Very rare	Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (see section **4.4**).
Immune system disorders	
Very rare	Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis (see section **4.4**).
Not known	Jarisch-Herxheimer reaction (see section **4.4**).
Nervous system disorders	
Very rare	Hyperkinesia, dizziness and convulsions (see section **4.4**).
Gastrointestinal disorders	
Clinical Trial Data	
*Common	Diarrhoea and nausea
*Uncommon	Vomiting
Post-marketing Data	
Very rare	Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis see section **4.4**). Black hairy tongue
Hepatobiliary disorders	
Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.
Skin and subcutaneous tissue disorders	
Clinical Trial Data	
*Common	Skin rash
*Uncommon	Urticaria and pruritus
Post-marketing Data	
Very rare	Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) (see section **4.4**), and drug reaction with eosinophilia and systemic symptoms (DRESS).
Renal and urinary tract disorders	
Very rare:	Interstitial nephritis Crystalluria (see section **4.4** and **4.9**)

*The incidence of these AEs was reported from clinical studies involving a total of approximately 6,000 adult and paediatric patients taking amoxicillin.

4.9 Overdose [4,5,6]

Esomeprazole

There is very limited experience reported 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.

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

Amoxicillin

Symptoms and signs of overdose
Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) 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 (see section **4.4** and **4.8**).

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.

5. PHARMACOLOGICAL PROPERTIES [4,5,6,7]

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

ATC code:

Esomeprazole

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 reported.

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, reported 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be

discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

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

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

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

Levofloxacin

Levofloxacin is a synthetic broad-spectrum antibacterial agent from the group of fluoroquinolones, containing as an active ingredient levofloxacin, a left rotating ofloxacin isomer.

Levofloxacin blocks DNA gyrase and topoisomerase IV, disrupts superhelix formation and cross-linking of DNA gaps, inhibits DNA synthesis, causes profound morphological changes in the cytoplasm, cell wall and membranes of microbial cells. Levofloxacin is active against most strains of microorganisms, both *in vitro* and *in vivo*.

In vitro

Susceptible microorganisms (MIC of ≤ 2 mg/L, inhibition zone ≥17 mm)

- Aerobic gram-positive microorganisms: *Bacillus anthracis, Corynebacterium diphtheriae, Corynebacterium jeikeium, Enterococcus faecalis, Enterococcus spp., Listeria monocytogenes, Staphylococcus coagulase-negative methi-S(I) [coagulase-negative susceptible/-modrate susceptible to methicillin)], Staphylococcus aureus methi-S (susceptible to methicillin), Staphylococcus epidermidis methi-S (susceptible to methicillin), Staphylococcus spp. CNS (coagulase-negative staphylococci), Streptococci of C u G groups, Streptococcus agalactiae, Streptococcus pneumoniae*

peni I/S/R (moderately susceptible/-susceptible/-resistant to penicillin), Streptococcus pyogenes, Viridans streptococci peni-S/R (susceptible/- resistant to penicillin).

- Aerobic *gram-negative microorganisms: Acinetobacter baumannii*, *Acinetobacter spp., Actinobacillus actinomycetemcomitans, Citrobacter freundii, Eikenella corrodens, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter spp., Escherichia coli, Gardnerella vaginalis, Haemophilus ducreyi, Haemophilus influenzae ampi-S/R (susceptible/-resistant to ampicillin), Haemophilus parainfluenzae, Helicobacter pylori, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella spp., Moraxella catarrhalis β+/β- (producing and non-producing beta-lactamases), Morganella morganii, Neisseria gonorrhoeae non PPNG/PPNG (not producing and producing penicillinase), Neisseria meningitidis, Pasteurella canis, Pasteurella dagmatis, Pasteurella multocida, Pasteurella spp., Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Providencia spp., Pseudomonas aeruginosa (hospital infections caused by Pseudomonas aeruginosa may require combined treatment), Pseudomonas spp., Salmonella spp., Serratia marcescens, Serratia spp.*
- Anaerobic microorganisms: *Bacteroides fragilis, Bifidobacterium spp., Clostridium perfringens, Fusobacterium spp., Peptostreptococcus, Propionibacterium spp., Veillonella spp.*
- Other microorganisms: *Bartonella spp., Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia trachomatis, Legionella pneumophila, Legionella spp., Mycobacterium spp., Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma hominis, Mycoplasma pneumoniae, Rickettsia spp., Ureaplasma urealyticum.*

(MIC = 4 mg/L, inhibition zone 16-14 mm)

- Aerobic gram-positive microorganisms: *Corynebacterium urealyticum, Corynebacterium xerosis, Enterococcus faecium, Staphylococcus epidermidis methi-R (resistant to methicillin), Staphylococcus haemolyticus methi-R (resistant to methicillin).*
- Aerobic gram-negative microorganisms*:* Campylobacter jejuni/coli.
- Anaerobic microorganisms: *Prevotella spp., Porphyromonas spp.*
- Resistant to levofloxacin microorganisms *(MIC ≥ 8 mg/L, inhibition zone ≤ 13 mm)*
- *Aerobic gram-positive microorganisms*: *Staphylococcus aureus methi-R (resistant to methicillin),*

Staphylococcus coagulase-negative methi-R (coagulase-negative, resistant to methicillin).

- Aerobic gram-negative microorganisms*:* Alcaligenes xylosoxidans.
- *Anaerobic microorganisms*: *Bacteroides thetaiotaomicron.*
- Other microorganisms*:* Mycobacterium avium.

Resistance

Resistance to levofloxacin develops as a result of a phased mutation process of genes encoding both topoisomerases of type II: DNA gyrase and topoisomerase IV. Other resistance mechanisms, such as the mechanism of influence on the penetration barriers of the microbial cell (the mechanism characteristic of *Pseudomonas aeruginosa*) and the mechanism of efflux (active excretion of the antimicrobial from the microbial cell) can also reduce the susceptibility of microorganisms to levofloxacin.

Due to the features of levofloxacin mechanism of action, there is usually no cross-resistance between levofloxacin and other antimicrobial agents.

Clinical efficacy (efficacy in clinical studies in treatment of infections caused by the microorganisms listed below)

- Aerobic gram-positive microorganisms*: Enterococcus faecalis, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes.*
- Aerobic gram-negative microorganisms*: Citrobacterfreundii, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella (Branhamella) catarrhalis, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens.*
- Others*: Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae*

Amoxicillin

Mechanism of action

Esomeprazole

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.

Pharmacokinetic/pharmacodynamic 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 main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- 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.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 5.0.

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacteriaceae	8[1]	8
Staphylococcus spp.	Note[2]	Note [2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note [4]	Note [4]
Streptococcus pneumoniae	Note [5]	Note [5]
Viridans group steprococci	0.5	2
Haemophilus influenzae	2[6]	2[6]
Moraxella catarrhalis	Note [7]	Note [7]
Neisseria meningitidis	0.125	1
Gram positive anaerobes except *Clostridiumdifficile*[8]	4	8
Gram negative anaerobes[8]	0.5	2
Helicobacter pylori	0.125[9]	0.125[9]
Pasteurella multocida	1	1
Non- species related breakpoints[10]	2	8

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L

[2]Most staphylococci are penicillinase producers, which are resistant to amoxicillin. Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactam agents.

[3]Susceptibility to amoxicillin can be inferred from ampicillin

[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility.

[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicillin avoid oral treatment with amoxicillin. Susceptibility inferred from the MIC of ampicillin.

[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be reported resistant.

[7]Beta lactamase producers should be reported resistant

[8]Susceptibility to amoxicillin can be inferred from benzylpenicillin.

[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguishwild-type isolates from those with reduced susceptibility.

[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3or 4 doses daily (1.5 to 2 g/day).

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

***In vitro* susceptibility of micro-organisms to Amoxicillin**
Commonly Susceptible Species
Gram-positive aerobes: *Enterococcus faecalis* Beta-hemolytic streptococci (Groups A, B, C and G) *Listeria monocytogenes*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli* *Haemophilus influenzae* *Helicobacter pylori* *Proteus mirabilis* *Salmonella* typhi *Salmonella* paratyphi *Pasteurella multocida*
Gram-positive aerobes: Coagulase negative staphylococcus *Staphylococcus aureus*£ *Streptococcus pneumoniae* Viridans group streptococcus
Gram-positive anaerobes: *Clostridium* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Other: *Borrelia burgdorferi*
Inherently resistant organisms†
Gram-positive aerobes: *Enterococcus faecium*†
Gram-negative aerobes: *Acinetobacter* spp. *Enterobacter* spp. *Klebsiella* spp. *Pseudomonas* spp.

Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

† Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ Almost all *S.aureus* are resistant to amoxilcillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

5.2 Pharmacokinetics 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 are reported approximately 1-2 hours after dose. The absolute bioavailability reported 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 reported on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is reported to be 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 reported 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 reported in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is 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 reported to be 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 reported 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 reported 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 reported 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 reported 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.

Elderly
The metabolism of esomeprazole is not reported 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 (t_{max}) in 12 to 18 year-olds was reported to be 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 been reported to have 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 100l after single and repeated 500mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:
Levofloxacin has been reported 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 and are 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 ($t_{½}$: 6 - 8 hours). 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 is reported to be affected by renal impairment. With decreasing renal function, renal elimination and clearance are decreased, and elimination half-lives increased as reported in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose is reported as below:

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 pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences

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

Amoxicillin

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

C_{max}	**T_{max} ***	**AUC $_{(0-24h)}$**	**T ½**
(µg/ml)	(h)	(µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56

*Median (range)

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as C_{max} and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is reported to be around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has 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 reported animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk (see section **4.6**).

Amoxicillin has been reported to cross the placental barrier (see section **4.6**).

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.

Elimination
The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is reported to be excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24 hour period.

Concomitant use of probenecid delays amoxicillin excretion (see section **4.5**).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. 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.

The **PYLOBACT NEO 2** is not recommended for use in pediatric patients (see section **4.2**).

Gender
Following oral administration of amoxicillin/ to healthy males and female subjects, gender has reported no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment
The total serum clearance of amoxicillin has been reported to be decreases proportionately with decreasing renal function (see section **4.2** and **4.4**).

It is recommended to avoid the use of **PYLOBACT NEO 2** in patients with renal impairment (see **section 4.2**).

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

It is recommended to avoid the use of **PYLOBACT NEO 2** in patients with hepatic impairment (see **section 4.2**).

5.3 Preclinical safety data

Esomeprazole

Reported 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 reported 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:

Reported 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 reported after long-term treatment in the rat with inhibitors of gastric acid secretion.

Amoxicillin

Reported non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Reported carcinogenicity studies have not been conducted with amoxicillin.

Levofloxacin

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

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

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

Reported studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not reported any genotoxic potential in a photo-mutagenicity assay, and it reduced tumour development in a photocarcinogenity study.

In common with other fluoroquinolones, levofloxacin reported 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 Film-coated Tablets: Microcrystalline cellulose, Hypermellose, Polysorbate 80, Purified water, Crospovidone, Magnesium stearate, Opadry yellow

Amoxicillin Film-coated Tablets: Microcrystalline cellulose, Sodium starch glycollate, Colloidal anhydrous silica, Purified talc, Magnesium stearate, Hypromellose, Titanium dioxide, Masking flavor Permaseal, Lake of sunset yellow, Polyethylene glycol 400, Purified water

Esomeprazole 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 at or below 30°C. Protect from moisture.

6.5 Nature and contents of container

Aluminium strip pack

6.6 Special precautions for disposal and other handling

Not Applicable

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited

8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

October 2019

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Information compiled in October 2019