Public Assessment Report

Decentralised Procedure

EVOXIL/LOVACIN/PRIXOTER/VOFLAN 5MG/ML SOLUTION FOR INFUSION

UK/H/1478, 80, 82 and 84/001/DC
UK Licence No: PL 17277/0035, 38, 41, 44

PHARMATHEN SA
LAY SUMMARY

On 24th March 2010, the UK granted Pharmathen SA Marketing Authorisations (licences) for the prescription only medicinal products Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion (PL 17277/0035, 38, 41 and 44; UK/H/1478, 80, 82 and 84/001/DC).

The active ingredient in this medicine is levofloxacin. Levofloxacin belongs to a group of medicines known as fluoroquinolone antibiotics, which kill bacteria.

Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets are used to treat infections caused by bacteria that are sensitive to levofloxacin.

Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets can be used to treat infections of the:
- Lungs, in people with long-term breathing problems or pneumonia
- Urinary tract, including your kidneys or bladder
- Prostate gland, where you have a long lasting infection
- Skin and underneath the skin, including muscles. This is sometimes called ‘soft tissue’.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion outweigh the risks; hence these Marketing Authorisations have been granted.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Levofloxacin hemihydrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5mg/ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Cyprus, Greece, Germany, Italy</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1478, 80, 82 and 84/001/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – 25&lt;sup&gt;th&lt;/sup&gt; February 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Evoxil/Prixoter/Lovacin/Voflan 5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for infusion contains 5 mg of Levofloxacin (as hemihydrate)
Each 50 ml vial of solution for infusion contains 250 mg of levofloxacin (as hemihydrate).
Each 100 ml vial of solution for infusion contains 500 mg of levofloxacin (as hemihydrate).

Excipients:
Each ml of solution for infusion contains 0.15 mmol (3.54 mg) sodium (as chloride)
50 ml of solution for infusion contains 7.70 mmol (177.10 mg) sodium (as chloride)
100 ml of solution for infusion contain 15.40 mmol (354.20 mg) sodium (as chloride)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for infusion.
A clear greenish-yellow solution, free from foreign particles.

pH: 4.5 – 5.1
Osmolality: 290 mOsmol/Kg ± 5%

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults for whom intravenous therapy is considered to be appropriate, Evoxil/Prixoter/Lovacin/Voflan solution for infusion is indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

• Community-acquired pneumonia (when it is inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection)
• Complicated urinary tract infections including pyelonephritis
• Chronic bacterial prostatitis.
• Skin and soft tissue infections. (see section 4.4)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Evoxil/Prixoter/Lovacin/Voflan is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. It is usually possible to switch from initial intravenous treatment to the oral route after a few days (Evoxil/Prixoter/Lovacin/Voflan 250 or 500 mg tablets), according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

TREATMENT TIME
The duration of therapy varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Evoxil/Prixoter/Lovacin/Voflan solution for infusion should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Method of administration
Evoxil/Prixoter/Lovacin/Voflan solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg Evoxil/Prixoter/Lovacin/Voflan solution for infusion (see section 4.4). It is possible to switch from an initial intravenous application to the oral route at the same dosage after a few days, according to the condition of the patient.
For incompatibilities see section 6.2 and compatibility with other infusion solutions see section 6.6.

**Posology:**

**Dosage in patients with normal renal function (creatinine clearance > 50 ml/min)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Daily dose regimen (depending on severity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia</td>
<td>500 mg once or twice daily</td>
</tr>
<tr>
<td>Complicated urinary tract infections including pyelonephritis</td>
<td>250 mg(^1) once daily</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>500 mg once daily</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>500 mg twice daily</td>
</tr>
</tbody>
</table>

\(^1\) Consideration should be given to increasing the dose in cases of severe infection.

**Special populations**

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

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose regimen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg/24 h</td>
<td>500 mg/24 h</td>
<td>500 mg/12 h</td>
</tr>
<tr>
<td>(\text{first dose:} 250\ mg)</td>
<td>(\text{first dose:} 500\ mg)</td>
<td>(\text{first dose:} 500\ mg)</td>
</tr>
<tr>
<td>50-20 ml/min</td>
<td>then: 125 mg/24 h then: 250 mg/24 h then: 250 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>(\text{then:} 125\ mg/48 h)</td>
<td>(\text{then:} 125\ mg/24 h)</td>
<td>(\text{then:} 125\ mg/12 h)</td>
</tr>
<tr>
<td>19-10 ml/min</td>
<td>then: 125 mg/48 h then: 125 mg/24 h then: 125 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>(&lt; 10\ ml/min) ((\text{including haemodialysis and CAPD}))</td>
<td>then: 125 mg/48 h then: 125 mg/24 h then: 125 mg/24 h</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

**Impaired hepatic function**

No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

**In the elderly**

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (see section 4.4 QT interval prolongation).

*Levofloxacin is contraindicated in children and growing adolescents (less than 18 years of age) (see section 4.3).*

### 4.3 Contraindications

Evoxil/Prixoter/Lovacin/Voflan solution for infusion must not be used:
- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents (up to age of 18),
- during pregnancy,
- in breast-feeding women.

### 4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia Evoxil/Prixoter/Lovacin/Voflan may not be the optimal therapy.

Nosocomial infections due to *P. aeruginosa* may require combination therapy.

**Infusion time**

The recommended infusion time of at least 30 minutes for 250mg or 60 minutes for 500mg Evoxil/Prixoter/Lovacin/Voflan solution for infusion should be observed. It is known for ofloxacin, that
during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (/-isomer of ofloxacin) the infusion must be halted immediately.

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 (see section 5.1).

**Tendinitis and tendon rupture**
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

**Clostridium difficile-associated disease**
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Evoxil/Prixoter/Lovacin/Voflan solution for infusion, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, levofloxacin for infusion must be stopped immediately and patients should be treated with supportive measures and specific therapy without delay (e.g. oral metronidazole or vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

**Patients predisposed to seizures**
Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous damage; concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with levofloxacin should be discontinued.

**Patients with glucose-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, and so levofloxacin should be used with caution.

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted in patients with renal impairment (see section 4.2).

**Hypersensitivity reactions**
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up 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.

**Hypoglycaemia**
As with all quinolones, hypoglycaemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

**Prevention of photosensitisation**
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), 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 4.8). 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 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).
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

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

Opiates
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 methods.

Hepatobiliary disorders
Cases of hepatic necrosis up to life-threatening 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.

This medicinal product contains 7.70 mmol (177.10 mg) sodium per 50 ml 15.40 mmol (354.20 mg) sodium per 100 ml of solution. This should be taken into account in patients on a controlled sodium diet and in cases where fluid restriction is required.

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

Effect of other medicinal products on levofloxacin
Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

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

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

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

Effect of levofloxacin on other medicinal products
Ciclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

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

4.6 Pregnancy and lactation
Pregnancy
Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women (see sections 4.3 and 5.3).

Lactation
In the absence of human data and due to the experimental 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).

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

4.8 Undesirable effects
The information given below is based on data from clinical studies in more than 5000 patients and on extensive post marketing experience.

The adverse reactions given below is based on data from clinical studies in more than 5000 patients and on extensive post marketing experience.

The adverse reactions are described according to the MedDRA system organ class 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)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Not known</td>
<td>Electrocardiogram QT prolonged (see section 4.4 QT interval prolongation and section 4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood and lymphatic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Leukopenia, eosinophilia</td>
</tr>
<tr>
<td>Rare</td>
<td>Thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Not known</td>
<td>Panacytopenia, haemolytic anaemia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td>Rare</td>
<td>Convulsion, tremor, paraesthesia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Sensory of sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Very rare Visual disturbance</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Very rare Convulsion, tremor, paraesthesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hearing impaired</td>
</tr>
<tr>
<td>Not known</td>
<td>Tinnitus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Very rare Pneumonitis allergic</td>
</tr>
<tr>
<td>Rare</td>
<td>Bronchospasm, dyspnoea</td>
</tr>
<tr>
<td>Very rare</td>
<td>Healthy</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Diarrhoea, nausea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vomiting, abdominal pain, dyspepsia, flatulence, constipation</td>
</tr>
<tr>
<td>Rare</td>
<td>Diarrhea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td>Very rare</td>
<td>Renal failure acute (e.g. due to nephritis interstitial)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Rash, pruritus</td>
</tr>
<tr>
<td>Rare</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Very rare</td>
<td>Angioneurotic oedema, photosensitivity reaction</td>
</tr>
<tr>
<td>Not known</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis. Mucocutaneous reactions may sometimes occur even after the first dose.</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Tendon rupture (see section 4.4). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis</td>
</tr>
<tr>
<td>Not known</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hypoglycaemia, particularly in diabetic patients</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fungal infection (and proliferation of other resistant microorganisms)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Hypotension</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Asthenia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Not known</td>
<td>Pain (including pain in back, chest and extremities)</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Anaphylactic shock (see section 4.4) Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.</td>
</tr>
<tr>
<td>Not known</td>
<td>Hypersensitivity (see section 4.4)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Not known</td>
<td>Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying</td>
</tr>
</tbody>
</table>
diseases (see section 4.4)

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Insomnia, nervousness</td>
</tr>
<tr>
<td>Rare</td>
<td>Psychotic disorder, depression, confusional state, agitation, anxiety</td>
</tr>
<tr>
<td>Very rare</td>
<td>Psychotic reactions with self-enduring behaviour including suicidal ideation or acts (see section 4.4), hallucinations</td>
</tr>
</tbody>
</table>

Other undesirable effects which have been associated with fluoroquinolone administration include:
- extrapyramidal symptoms and other disorders of muscular coordination,
- hypersensitivity vasculitis,
- attacks of porphyria in patients with porphyria.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supratherapeutic doses, the most important signs to be expected following acute overdosage of Evoxil/Prixoter/Lovacin/Voflan solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.

No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones

ATC code: J01MA12

Levofoxacin 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 (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

The main mechanism of resistance is due to a gyr-A mutation. In vitro there is a cross-resistance between levofloxacin and other fluoroquinolones.

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

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediate susceptible organisms and intermediate susceptible from resistant organisms are presented in the below table for MIC testing (mg/L):

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecobacteriaceae</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>S.pneumoniae</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Streptococcus A, B, C, G</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
</tbody>
</table>

EUCAST clinical MIC breakpoints for levofloxacin (2009-04-07):
The S/I-breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints relate to high dose therapy.

Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.

Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table.

The CLSI (Clinical and Laboratory Standards Institute, formerly NCCLS) recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (μg/mL) or disc diffusion testing (zone diameter [mm] using a 5 μg levofloxacin disc).

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Non Enterobacteriaceae</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>≤1 μg/mL</td>
<td>≥4 μg/mL ≤15 mm</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
<tr>
<td>Beta-haemolytic Streptococcus</td>
<td>≤2 μg/mL</td>
<td>≥8 μg/mL ≤13 mm</td>
</tr>
</tbody>
</table>

1 The absence of rare occurrence of resistant strains precludes defining any results categories other than ‘susceptible’. For strains yielding results suggestive of a ‘non-susceptible’ category, organism identification and antimicrobial susceptibility test results should be confirmed by a reference laboratory using CLSI reference dilution method.

Antibacterial spectrum
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.

COMMONLY SUSCEPTIBLE MICROORGANISMS

**Aerobic Gram-positive bacteria**
- Staphylococcus aureus* methicillin susceptible
- Staphylococcus saprophyticus
- Streptococci, groups C and G
- Streptococcus agalactiae
- Streptococcus pneumoniae*
- Streptococcus pyogenes*

**Aerobic Gram-negative bacteria**
- Burkholderia cepacia*
- Eikebella corrodens
- Haemophilus influenzae*
- Haemophilus para-influenzae*
- Klebsiella oxytoca
Klebsiella pneumoniae*
Moraxella catarrhalis*
Pasteurella multocida
Proteus vulgaris
Providencia rettgeri

**Anaerobic bacteria**
Peptostreptococcus

**Other**
Chlamydophila pneumoniae*
Chlamydophila psittaci
Chlamydia trachomatis
Legionella pneumophila*
Mycoplasma pneumoniae*
Mycoplasma hominis
Ureaplasma urealyticum

**SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM**

**Aerobic Gram-positive bacteria**
Enterococcus faecalis*
Staphylococcus aureus methicillin-resistant
Staphylococcus haemolyticus methicillin resistant

**Aerobic Gram-negative bacteria**
Acinetobacter baumannii*
Citrobacter freundii*
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae*
Escherichia coli*
Morganella morganii*
Proteus mirabilis*
Providencia stuartii
Pseudomonas aeruginosa*
Serratia marcescens*

**Anaerobic bacteria**
Bacteroides fragilis
Bacteroides ovatus$
Bacteroides thetaiotaomicron$
Bacteroides vulgatus$
Clostridium difficile$

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
$ Natural intermediate susceptibility
+ More than 50% of resistance

**Other information**
Nosocomial infections due to *P. aeruginosa* may require combination therapy.

**5.2 Pharmacokinetic properties**

**Absorption**
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is approximately 100%. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg. Food has little effect on the absorption of levofloxacin.
Distribution
Approximately 30 - 40 % of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

Penetration into tissues and body fluids:
Penetration into Bronchial Mucosa, Epithelial Lining Fluid (ELF)
Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after 500 mg p.o. were 8.3 μg/g and 10.8 μg/ml respectively. These were reached approximately one hour after administration.

Penetration into Lung Tissue
Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 μg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.

Penetration into Blister Fluid
Maximum levofloxacin concentrations of about 4.0 and 6.7 μg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily, respectively.

Penetration into Cerebro-Spinal Fluid
Levofloxacin has poor penetration into cerebro-spinal fluid.

Penetration into prostatic tissue
After administration of oral 500mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7 μg/g, 8.2 μg/g and 2.0 μg/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

Concentration in urine
The mean urine concentrations 8 -12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively.

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). 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 600 mg.

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:

<table>
<thead>
<tr>
<th>Clcr [ml/min]</th>
<th>&lt; 20</th>
<th>20 - 40</th>
<th>50 - 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClR [ml/min]</td>
<td>13</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>t1/2 [h]</td>
<td>35</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

Elderly patients
There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with differences in creatinine clearance.
Gender differences
Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

Acute toxicity
The median lethal dose (LD_{50}) values obtained in mice and rats after intravenous administration of levofloxacin were in the range 250-400mg/kg mg/kg; in dogs the LD_{50} value was approximately 200mg/kg with one of two animals which received this dose dying.

Repeated dose toxicity
Studies of one and six months duration with intravenous administration have been carried out in the rat (20, 60, 180 mg/kg/day) and monkey (10,25 63 mg/kg/day) and a three-month study has also been carried in the rat (10, 30, 90 mg/kg/day). The No Observed Adverse Effect Levels (NOELs) in the rat studies were concluded to be 20 and 30 mg/kg/day in the one-month and three-month studies respectively. Crystal deposits in urine were seen in both studies at doses of 20 mg/kg/day and above. High doses (180 mg/kg/day for 1 month or 30 mg/kg/day and above for 3 months) slightly decreased food consumption and body weight gain. Haematological examination showed reduced erythrocytes and increased leucocytes and reticulocytes at the end of the 1 month, but not the 3 months study. The NOELs in the monkey study were concluded to be 63 mg/kg/day with only minor reduction in food and water consumption at this dose.

Reproductive toxicity
Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day or intravenous doses up to 100 mg/kg/day. Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day. Levofloxacin had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

Genotoxicity
Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung (CHL) cells in vitro at or above 100 μg/ml, in the absence of metabolic activation. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Phototoxic potential
Studies in the mouse after both intravenous and oral dosing showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity assay.

Carcinogenic potential
No indication of carcinogenic potential was seen in a two year study in the rat with dietary administration (0, 10, 30 and 100 mg/kg/day).

Toxicity to joints
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
Sodium chloride
Hydrochloric acid 5N (for pH adjustment)
Water for injection

6.2 Incompatibilities
Evoxil/Prixoter/Lovacin/Voflan solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life as packaged for sale: 36 months
Shelf life after removal of the outer packaging: 3 days (under indoor light conditions)
Shelf life after perforation of the rubber stopper: (see 6.6)

After first opening:
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Keep container in the outer carton in order to protect from light.

6.5 Nature and contents of container

50 ml, type I transparent glass vial sealed with bromobutyl rubber stopper and an aluminium cap. Each vial contains 50 ml solution. Packs of 1 and 5 and 20 vials are available.

100ml, type I transparent glass vial sealed with bromobutyl rubber stopper and an aluminium cap. Each vial contains 100ml solution. Packs of 1, 5 and 20 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused solution.

The product should be inspected visually for particles and discoloration prior to administration. Only clear greenish-yellow solution free from particles should be used.

Evoxil/Prixoter/Lovacin/Voflan solution for infusion should be used immediately (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

This medicine may be given alone or with one of the following solutions:
- 0.9% sodium chloride solution
- 5% dextrose injection
- 2.5% dextrose in Ringer solution
- Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes)

Chemical and physical compatibility of Levofloxacin Solution for Infusion with the above solutions have been demonstrated for 4 hours at room conditions.

See section 6.2 for incompatibilities.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece
tel.: +30 210 666 4300
fax: +30 210 666 6749
e-mail: info@pharmathen.com

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0035, 38, 41 and 44

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/03/2010

10 DATE OF REVISION OF THE TEXT
24/03/2010
Module 3
Product Information Leaflet

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product. Please note that the PIL text below is for Evoxil 5mg/ml Solution for Infusion. Other PILs are available for Lovacin, Prixoter and Voflan 5mg/ml Solution for Infusion.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Evoxil 5 mg/ml solution for infusion
Levofloxacin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT Evoxil IS AND WHAT IT IS USED FOR
2. BEFORE YOU USE Evoxil
3. HOW TO USE Evoxil
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE Evoxil
6. FURTHER INFORMATION

1. WHAT Evoxil IS AND WHAT IT IS USED FOR

The active substance in the solution is levofloxacin. Levofloxacin belongs to a group of medicines known as fluoroquinolone antibiotics, which kill bacteria.

Evoxil solution for infusion is used to treat infections caused by bacteria that are sensitive to levofloxacin. Your doctor will have decided if your infection can be treated with this medicine. Evoxil can be used to treat infections of the:
- Lungs, in people with long-term breathing problems or pneumonia
- Urinary tract, including your kidneys or bladder
- Prostate gland, where you have a long lasting infection
- Skin and underneath the skin, including muscles. This is sometimes called ‘soft tissue’.

2. BEFORE YOU USE EVOXIL

Do not receive Evoxil
- if you are allergic (hypersensitive) to Levofloxacin or to other active substances that belong to the same group of antibiotics (i.e. quinolones) or to any of the other ingredients of the medicine.
- if you suffer from epilepsy. Otherwise, your risk of getting “fits” (convulsions) is increased.
- if you had ever had tendon problems (e.g. tendinitis) relating to treatment with an active substance that belongs to the same class of antibiotics (i.e. fluoroquinolones).
- if you are pregnant or planning to become pregnant or if you are breast-feeding.
- if the solution for infusion has been prescribed to children or growing teenagers. It could harm the cartilage of their growing bones. The solution is only intended for adults.
Tell your doctor if you have had any problems with taking medicines in the past.

**Take special care with Evoxil**

- The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg Levofloxacin solution for infusion should be observed. During the infusion time, the patient should be examined for a potent tachycardia (rapid heart beat) and a temporary decrease in blood pressure. In rare cases, as a consequence of a profound drop in blood pressure, circulatory problems may occur.

- if you have experienced “fits” or brain damage in the past (such as stroke or severe brain injury). Make sure your doctor knows about your medical history, so he can give you appropriate advice.

- when you are exposed to sunlight or UV light. Do not stay out in strong sunlight for unnecessarily long periods and do not use a sun-lamp or solarium. Your skin may become more sensitive to light while using this medicine (may cause sunburn – like reactions).

- if you get pain or inflammation in your tendons, particularly if you are elderly or taking any medicines known as corticosteroids (cortisone or similar medicines used as anti – inflammatories in many disorders such as asthma, allergic conditions/reactions and arthritis). If you experience any tendon complaints during or shortly after receiving this medicine you should seek medical advice immediately and rest the affected limb to avoid tendon damage. Do not take the next dose unless your doctor tells you to.

- if you have severe, persistent and/or bloody diarrhoea during or after treatment with this medicine. This may be a sign of serious bowel inflammation ( pseudomembranous colitis) which can occur following treatment with antibiotics. Tell your doctor immediately. It may be necessary to stop treatment and start specific therapy.

- if you have a family history of or have an actual defect in the liver enzyme called glucose-6-phosphate dehydrogenase (G6PD) (a rare hereditary disease). Patients with G6PD deficiency may be prone to destruction of red blood cells (haemolysis) when treated with quinolone antibacterial agents.

- if you suffer from kidney problems. Patients with reduced kidney activity (renal insufficiency) may need lower doses than patients with normal kidney activity.

- if you are taking any medicines which thin the blood (known as anti – coagulants e.g. warfarin).

- if you have a history of psychiatric disease. Tell your doctor immediately if you experience a psychotic reaction.

- if you have ever had symptoms due to nerve damage such as kinetic or sensory problems in hand and feet , that are more severe at night

- if you have ever had heart problems.

- if you are diabetic and you receive concomitant treatment with an oral medicine that lowers blood levels of glucose.

- if you have ever had liver problems. You should stop treatment and contact your doctor immediately if symptoms of liver disease develop such as reduced appetite, jaundice, dark urine, itching or gastrointestinal disturbances.

- if you have allergic reactions to the medicine. In that case, you should stop treatment immediately and contact your doctor or an emergency doctor.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without prescription, including herbal medicines. Some medicines can interfere with your treatment or alter blood levels of those medicines you are currently taking, so make sure to check with your doctor or pharmacist before taking any
other medications whether prescribed by a doctor or bought by you over the counter. In particular tell your doctor if you are taking any of the following:

- Vitamin K antagonists such as warfarin. In combination with Levofloxacin may lead to an increase in bleeding.
- theophylline (used to treat asthma) or fenbufen or similar medicines (used against rheumatic pain and inflammation). The risk of getting “fits” may be increased.
- probenecid (used to prevent gout) or cimetidine (used to treat ulcers) reduce your kidneys ability to get rid of levofloxacin. This is unlikely to have any clinical relevance.
- ciclosporin (used to treat psoriasis, dermatitis, rheumatism). The effect of this active substance may be prolonged if used in combination with Levofloxacin.
- Corticosteroids, sometimes called steroids – used for inflammation. You may be more likely to have inflammation and/or breakage of your tendons.
- Non-steroidal anti-inflammatory drugs (NSAIDS) – used for pain and inflammation such as aspirin, ibuprofen, fenbufen, ketoprofen and indomethacin. You are more likely to have a fit (seizure) if taken with Evoxil.
- Medicines known to affect the way your heart beats. This includes medicines used for abnormal heart rhythm (antiarrhythmics such as quinidine and amiodarone), for depression (tricyclic antidepressants such as amitriptyline and imipramine,) and for bacterial infections (‘macrolide’ antibiotics such as erythromycin, azithromycin and clarithromycin).

Using Levofloxacin with food and drink
Ask your doctor for advice before taking any medicine. Inform your doctor before you receive levofloxacin and follow his/her instructions.

Pregnancy and Breast-feeding
Do not use Levofloxacin if you are pregnant or breast feeding a baby. It could harm your baby. Ask your doctor for advice before taking any medicine.

Driving and using machines
Some side – effects like dizziness, drowsiness and visual disturbances may impair your ability to concentrate and react. Do not drive, operate dangerous machinery or have similar activities if you feel that your ability to concentrate and react is impaired.

Important information about some of the ingredients in Levofloxacin Solution for Infusion
This medicinal product contains sodium chloride (salt). It contains 0.15 mmol (or 3.54 mg) of sodium per ml of infusion (a total of 7.70 mmol or 177.10 mg sodium in 50 ml, a total of 15.40 mmol or 354.20 mg sodium in 100ml). This should be taken into consideration by patients on a controlled sodium diet and in cases where fluid restriction is required.

3. HOW EVOXIL IS GIVEN
Evoxil is given intravenously (by slow infusion into a vein) and administered to you by your doctor or nurse.

The dosage of levofloxacin is determined by the type and severity of the infection. Your doctor or nurse will decide how to give your medicine.

*The dose in adults and the elderly with normal kidney function is 250 mg- 500 mg once or twice daily.*
Your doctor will reduce the dose or the frequency with which levofloxacin is given if you have any kidney problems.

The duration of treatment is determined according to your clinical condition and your response to treatment. As with all antibacterial agents, treatment with Levofloxacin should be continued for at least 2 to 3 days after body temperature has returned to normal and the symptoms have subsided.
Once your condition has improved, the way your treatment is given may be changed from an infusion into a vein to tablets given orally at the same daily dose.

If you receive more Evoxil than you should
Your doctor or nurse will ensure that you will receive the correct dose into the vein. Symptoms of an accidental overdose might result in central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and (convulsive) fits and heart disorders, possibly leading to abnormal heart rhythm. Consult your doctor if you think you have been administered more Levofloxacin than you should.

If you forget to use Evoxil
If you think that you may have missed a dose talk to your doctor or nurse. You should not have a double dose to make up for a forgotten dose.

If you stop using Evoxil
Your doctor may decide to stop treatment into a vein and ask you to continue treatment with Levofloxacin Tablets.
If you still feel unwell at the end of your prescribed course of treatment, tell your doctor.

If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all other medicines Levofloxacin can cause side effects although not everybody gets them. The side effects in this section are given with an estimation of the frequency with which they may occur.

Severe allergic reactions can occur very rarely. These can happen after the first dose or even after treatment has stopped. If you get any of these side effects while having your medicine, stop having <Levofloxacin> immediately and tell your doctor or go to the nearest hospital casualty department. Signs of an allergic reaction are:
- fast heart rate, low blood pressure, fever, breathing problems, shock,
- swelling of the face, tongue and throat, skin reactions such as swelling and redness, blood problems, ulcers in the mouth, eyes, gut and genital organs,
- Severe liver problems can develop in some people. Signs of liver problems include yellow skin, dark urine, stomach tenderness and loss of appetite.
- Unaccountable muscle pain, muscle weakness muscle cramps.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>common</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>uncommon</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>rare</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>very rare</td>
<td>affects less than 1 user in 10,000</td>
</tr>
</tbody>
</table>
not known: frequency cannot be estimated from the available data

Other side effects include

Common side effects:
- Nausea, diarrhoea
- Increase in blood levels of liver enzymes

Uncommon side effects:
- Itching and rash
- Loss of appetite, stomach upset (dyspepsia), vomiting or pain in the abdominal region
- Headache, dizziness, drowsiness, sleeping problems
- Increase or decrease in the number of white blood cells
- General weakness. Any antibacterial treatment that kills certain germs may lead to a disturbance of the micro-organisms (bacteria / fungi) that are normally found in humans. Consequently, the number of other bacteria or fungi may increase, which in rare cases requires treatment

Rare side effects:
General allergic reactions (anaphylactic / anaphylactoid reactions) (which may sometimes occur even after the first dose and which may develop fast within minutes or hours of intake) with symptoms such as hives (urticaria), cramping of the bronchi and possibly severe breathing problems, as well as in very rare cases swelling of the skin and mucous membranes (e.g. in the face and throat)
- Bloody diarrhoea which in very rare cases may be indicative of enterocolitis (inflammation of the bowel), including pseudomembranous colitis (inflammation of the large intestine)
- Feeling a tingling sensation, e.g. in the hands (paraesthesia), trembling, “fits” (convulsions) and confusion
- Anxiety, depression, psychotic reactions, restlessness (agitation)
- Abnormally rapid beating of the heart, abnormally low blood pressure
- Tendon pain and inflammation (tendonitis), joint pain or muscle pain
- Decrease in the number of blood platelets leading to tendency to bruise and bleed easily

Very rare side effects:
- Sudden drop in blood pressure or collapse (shock), mild skin reactions, increased sensitivity of the skin to sun and ultraviolet light
- Decrease in blood sugar to a too low level (hypoglycaemia) which may be of special importance in patients treated for diabetes, attacks of porphyria in patients with porphyria (a very rare metabolic disease)
- Vision and hearing disorders, disturbances of taste and smell, numbness, disorders of movement, including walking difficulties.
- Hallucinations, psychotic reactions with risk of suicidal thoughts or actions.
- Circulatory collapse (anaphylactic like shock).
- Tendon rupture (e.g.: Achilles tendon), which may occur within 48 hours after starting treatment and may be bilateral, muscular weakness, which may be of special importance in patients with myasthenia gravis (a rare disease of the nervous system)
- Severe decrease in the number of white blood cells (agranulocytosis) leading to symptoms such as recurrence or persistence of fever, sore throat and feeling more ill again
- Inflammation of the liver; disturbances of kidney function and occasional kidney failure due to allergic kidney reactions (interstitial nephritis).
- Fever, allergic inflammation of small blood vessels or allergic lung reactions.

Isolated cases: even more rare side effects
- Severe blistering reactions of the skin and mucous membranes (Steven’s Johnson syndrome), toxic epidermal necrolysis (Lyell’s syndrome) and erythema exsudativum multiforme.
- Heart disorders, possibly leading to abnormal heart rhythm.
- Muscle reactions with muscle cell damage (rhabdomyolysis).
- Decrease in red blood cells (anaemia) due to blood cell damage, decrease in the number of all types of blood cells.

Evoxil may cause a reduction in the number of white blood cells and your resistance to infection may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell you doctor or your pharmacist.

5. HOW TO STORE EVOXIL

Keep out of the reach and sight of children.
Your doctor or nurse will ensure that Levofloxacin is properly stored. As with all medicines it must be kept out of the reach of children.
This medicine should be kept in its cardboard box for protection from light until use. No protection from light is required during infusion, or within three days after removal from the outer packaging if stored under indoor light conditions. Once the infusion bottle has been opened (rubber stopper perforated) the solution should be used immediately (within 3 hours) in order to prevent any bacterial contamination.
Do not use this medicine after the expiry date shown on the packaging. The expiry date refers to the last day of the month.
Medicines should not be disposed of via the wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Levofloxacin contains
The active substance is levofloxacin (as hemihydrate).
One ml solution for infusion contains 5 mg of levofloxacin. Each 50 ml vial of solution for infusion contains 250 mg of levofloxacin and each 100 ml vial of solution for infusion contains 500 mg of levofloxacin.

The other ingredients are: Sodium Chloride,
Hydrochloric Acid (for pH adjustment) and
Water for Injection

What Levofloxacin looks like and contents of the pack
# Module 4
## Labelling

The labelling below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

Please note that the label text below is for Evoxil 5mg/ml Solution for Infusion. Other label texts are available for Lovacin, Prixoter and Voflan 5mg/ml Solution for Infusion.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</th>
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</thead>
<tbody>
<tr>
<td>Box (50ml vial)</td>
</tr>
<tr>
<td>50 ml Vial label</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Evoxil 5 mg/ml Solution for Infusion
Levofoxacin

2. **STATEMENT OF ACTIVE SUBSTANCE**

Each ml of solution for infusion contains 5 mg of Levofoxacin (as hemihydrate).
Each vial of 50 ml solution for infusion contains 250 mg of levofloxacin.

3. **LIST OF EXCIPIENTS**

Also contains sodium chloride, hydrochloric acid, water for injection.
See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion
1 vial of 50 ml
5 vials of 50 ml
20 vials of 50 ml

5. **METHOD AND ROUTE OF ADMINISTRATION**

For intravenous use. For single use only. Discard any remaining solution.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Only clear and greenish-yellow solution should be used.

8. **EXPIRY DATE**

EXP: {MM/YYYY}
To be used immediately (within 3 hours) after perforation of the rubber stopper.
To be used within 3 days (under indoor light conditions) after removal of the outer carton.

9. **SPECIAL STORAGE CONDITIONS**

Keep the container in the outer carton in order to protect from light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece
tel.: +30 210 666 4300
fax: +30 210 666 6749
e-mail: info@pharmathen.com

12. MARKETING AUTHORISATION NUMBER

PL 17277/0035

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by a doctor

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Box (100ml vial)
100ml Vial label

1. NAME OF THE MEDICINAL PRODUCT

Evoxil 5 mg/ml Solution for Infusion
Levofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE

Each ml of solution for infusion contains 5 mg of Levofloxacin (as hemihydrate).
Each vial of 100 ml solution for infusion contains 500 mg of levofloxacin.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, hydrochloric acid, water for injection.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial of 100 ml
5 vials of 100 ml
20 vials of 100 ml

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use. For single use only. Discard any remaining solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only clear and greenish-yellow solution should be used.

8. EXPIRY DATE

EXP: [MM/YYYY]
To be used immediately (within 3 hours) after perforation of the rubber stopper.
To be used within 3 days (under indoor light conditions) after removal of the outer carton.

9. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton in order to protect from light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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POM

15. INSTRUCTIONS ON USE

Use as directed by a doctor

16. INFORMATION IN BRAILLE
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Cyprus, Germany, Greece, Italy and the UK considered that the applications for Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion could be approved. These products are prescription only medicines (POM) and are indicated in adults for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Community-acquired pneumonia (*when it is inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection*)
- Complicated urinary tract infections including pyelonephritis
- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

These applications for Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to the reference product being Tavanic 5mg/ml Solution for Infusion, first authorised in the UK to Hoechst Marion Roussel Limited in June 1997.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies have been performed and none are required for these applications as the pharmacology of levofloxacin hemihydrate is well-established.

For manufacturing sites within the Community, the Reference Member State (RMS) has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a Qualified Person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a risk management plan (RMP).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Levofloxacin hemihydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antinfectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones (J01MA12)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>5mg/ml Solution for Infusion</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1478, 80, 82 and 84/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Cyprus, Greece, Germany, Italy</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17277/0035, 38, 41, 44</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pharmathen S.A., Dervenakion 6, 15351 Pallini, Attiki, Greece</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Levofloxacin hemihydrate

Chemical name: \((-\)-(s)-\)9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoazine-6-carboxylic acid hemihydrate.

Structural formula:

![Structural formula of Levofloxacin hemihydrate]

Molecular formula: C\(_{18}\)H\(_{20}\)FN\(_3\)O\(_4\)·\(\frac{1}{2}\)H\(_2\)O

Appearance: Almost white or light yellow crystalline powder

Solubility: Sparingly soluble in water, soluble in methylene chloride and acetic acid

Molecular weight: 370.38

Levofloxacin hemihydrate complies with specification in the US Pharmacopoeia forum.

A Drug Master File (DMF) has been provided covering the manufacture and control of the active substance levofloxacin hemihydrate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance levofloxacin hemihydrate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients sodium chloride, hydrochloric acid 5N and water for injections, which complies with its European Pharmacopoeia monograph. None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to produce products that could be considered generic medicinal products of Tavanic 5mg/ml Solution for Infusion.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference product.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three pilot-scale batches have been provided. The applicant has committed to perform process validation on the first three production-scale batches of each strength.

**Finished Product Specification**

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working reference standards used.

**Container-Closure System**

The product is packaged in glass vials composed of Type I transparent glass with a bromobutyl rubber stopper and covered with an aluminium cap. The vials come in sizes of 50ml and 100ml. Pack sizes of 1, 5 and 20 vials are available.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

**Stability of the product**

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 36 months for an unopened product with storage condition “Keep container in the outer carton in order to protect from light”.

Once the product has been removed from the outer packaging, it can be kept for up to 3 days (under indoor light conditions).
The product should be used immediately (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion. Unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**

The SPCs, PIL and labelling are pharmaceutically acceptable. User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA form**

The MAA forms are pharmaceutically satisfactory.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

The grant of Marketing Authorisations is recommended.
III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of levofloxacin hemihydrate are well-known. As levofloxacin hemihydrate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
III.3 CLINICAL ASPECTS

1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
No bioequivalence studies have been performed and none are required for these applications, as the applicant’s product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically in vivo. A human bioavailability study is not relevant to this application as the compound is intended for intravenous infusion.

3. Post marketing experience
Levofloxacin hemihydrate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the Marketing Authorisations is supported.

4. Benefit-Risk assessment
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with levofloxacin hemihydrate is considered to have demonstrated the therapeutic value of both compounds. The risk benefit is, therefore, considered to be positive.

5. Conclusions
The grant of Marketing Authorisations for Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Evoxil/Lovacin/Prixoter/Voflan 5mg/ml Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

CLINICAL
No bioequivalence studies have been performed and none are required for these applications, given the composition of the product and its intended route of administration.
No new or unexpected safety concerns arise from these applications.
The SPCs, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with levofloxacin hemihydrate is considered to have demonstrated the therapeutic value of both compounds. The risk benefit is, therefore, considered to be positive.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
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