Public Assessment Report

Decentralised Procedure

EVOXIL/LOVACIN/PRIXOTER/VOFLAN/XAVEL 250MG AND 500MG FILM-COATED TABLETS

UK/H/1477, 81, 79, 83, 2198/001-2/DC
UK Licence No: PL 17277/0033-4, 36-7, 39-40, 42-3, 70-1

PHARMATHEN SA
LAY SUMMARY

On 12th March 2010, the UK granted Pharmathen SA Marketing Authorisations (licences) for the prescription only medicinal products Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets (PL 17277/0033-4, 36-7, 39-40, 42-3, 70-1; UK/H/1477, 81, 79, 83, 2198/001-2/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:
- Sinuses
- 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/Xavel 250mg and 500mg film-coated Tablets 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/Xavel 250mg and 500mg film-coated Tablets</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>film-coated Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>250mg and 500mg</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/1477, 81, 79, 83, 2198/001-2/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – February 2010</td>
</tr>
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</table>
# Module 2

## Summary of Product Characteristics

<table>
<thead>
<tr>
<th>1</th>
<th>NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evoxil/Lovacin/Prixoter/Voflan/Xavel 250 mg film-coated tablets</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>QUALITATIVE AND QUANTITATIVE COMPOSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains levofloxacin hemihydrates equivalent to 250 mg of levofloxacin</td>
<td></td>
</tr>
<tr>
<td>Excipients:</td>
<td></td>
</tr>
<tr>
<td>Each tablet contains the excipient FD&amp;C yellow #6/Sunset Yellow aluminum lake.</td>
<td></td>
</tr>
<tr>
<td>For a full list of excipients, see section 6.1.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>PHARMACEUTICAL FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film-coated tablet.</td>
<td></td>
</tr>
<tr>
<td>Pink, oblong, biconvex film-coated tablet with a scoreline.</td>
<td></td>
</tr>
<tr>
<td>The tablet can be divided into equal halves.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4</th>
<th>CLINICAL PARTICULARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Therapeutic indications</td>
<td></td>
</tr>
<tr>
<td>In adults with infections of mild or moderate severity, Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:</td>
<td></td>
</tr>
<tr>
<td>• Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),</td>
<td></td>
</tr>
<tr>
<td>• Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),</td>
<td></td>
</tr>
<tr>
<td>• Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),</td>
<td></td>
</tr>
<tr>
<td>• Uncomplicated urinary tract infections</td>
<td></td>
</tr>
<tr>
<td>• Complicated urinary tract infections (including pyelonephritis)</td>
<td></td>
</tr>
<tr>
<td>• Chronic bacterial prostatitis.</td>
<td></td>
</tr>
<tr>
<td>• Skin and soft tissue infections.</td>
<td></td>
</tr>
<tr>
<td>Consideration should be given to official guidance on the appropriate use of antibacterial agents.</td>
<td></td>
</tr>
</tbody>
</table>

| 4.2 Posology and method of administration |
|---|---|
| Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets are administered once or twice daily. |
| The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. |
| Treatment time |
| The duration of therapy varies according to the course of the disease (see table below). |
| As with antibiotic therapy in general, administration of Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. |
| Method of administration |
| Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals. |
Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets should be taken at least two hours before iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

**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>
<th>Duration of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial sinusitis</td>
<td>500 mg once daily</td>
<td>10 - 14 days</td>
</tr>
<tr>
<td>Acute bacterial exacerbations of chronic bronchitis</td>
<td>250 to 500 mg once daily</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>500 mg once or twice daily</td>
<td>7 - 14 days</td>
</tr>
<tr>
<td>Uncomplicated urinary tract infections</td>
<td>250 mg once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Complicated urinary tract infections including pyelonephritis</td>
<td>250 mg once daily</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>500 mg once daily</td>
<td>28 days</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>250 mg once daily or 500 mg once or twice daily</td>
<td>7 - 14 days</td>
</tr>
</tbody>
</table>

**Special populations**

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

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>500 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>500 mg/12 h</td>
</tr>
<tr>
<td>250 mg/24 h</td>
<td>500 mg/24 h</td>
</tr>
<tr>
<td>250 mg/12 h</td>
<td>500 mg/24 h</td>
</tr>
<tr>
<td>first dose: 250 mg</td>
<td>first dose: 500 mg</td>
</tr>
<tr>
<td>then: 125 mg/24 h</td>
<td>then : 250 mg/24 h</td>
</tr>
<tr>
<td>then : 250 mg/12 h</td>
<td>then: 250 mg/24 h</td>
</tr>
<tr>
<td>50-20 ml/min</td>
<td>then: 125 mg/48 h</td>
</tr>
<tr>
<td>19-10 ml/min</td>
<td>then : 125 mg/ 24 h</td>
</tr>
<tr>
<td>&lt; 10 ml/min (including haemodialysis and CAPD) 1</td>
<td>then: 125 mg/48 h</td>
</tr>
<tr>
<td>then: 125 mg/24 h</td>
<td>then : 125 mg/24 h</td>
</tr>
<tr>
<td>then: 125 mg/24 h</td>
<td>then: 125 mg/24 h</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).

**In children**

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

**Contraindications**

Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets must not be used:
- in patients hypersensitive to levofloxacin, other quinolones or any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents (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 levofloxacin may not be the optimal therapy. Nosocomial infections due to *P. aeruginosa* may require combination therapy.

*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).

*In infections suspicious for MRSA levofloxacin should be combined with an agent approved to treat MRSA infections.*

*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/Lovacin/Prixoter/Voflan/Xavel tablets, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets 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 system 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 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.

*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., glinidemide) or with insulin. In these diabetic patients, careful monitoring of blood glucose in 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 or 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 Evoxil/Lovacin/Prixoter/Voflan/Xavel in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly (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, 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 the colouring agent sunset yellow (E110), which may cause allergic reactions.

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
Iron salts, magnesium- or aluminium-containing antacids
Levofloxacin absorption is significantly reduced when iron salts, buffered formulations or magnesium- or aluminium-containing antacids are administered concomitantly. It is recommended that preparations containing divalent or trivalent cations such as iron salts, buffered formulations or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after Evoxil/Lovacin/Prixoter/Voflan/Xavel tablet administration. No interaction was found with calcium carbonate.

Sucralfate
The bioavailability of Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration (see section 4.2).
Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.
Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

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

Other forms of interactions
Meals
There is no clinically relevant interaction with food. Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets may therefore be administered regardless of food intake.

4.6 Pregnancy and lactation
Pregnancy
The product is contraindicated during 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 section 4.3 and 5.3).

Lactation
The product is contraindicated in breast-feeding women. 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 are described according to the MedDRA system organ class below.

Frequencies are defined using the following convention:

- Very common (≥1/10)
- Common (≥1/100, <1/10)
- Uncommon (≥1/1,000, <1/100)
- Rare (≥1/10,000, <1/1,000)
- Very rare (<1/10,000)

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

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td></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 system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not Known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not Known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Not Known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not Known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
</tr>
</tbody>
</table>

**Cardiac disorders**

**Blood and lymphatic system disorders**

**Nervous system disorders**

**Eye disorders**

**Ear and labyrinth disorders**

**Respiratory, thoracic and mediastinal disorders**

**Gastrointestinal disorders**

**Renal and urinary disorders**

**Skin and subcutaneous tissue disorders**

**Musculoskeletal and connective tissue disorders**
### Very rare
- 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Known</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

### Metabolism and nutrition disorders
- Anorexia

### Infections and infestations
- Fungal infection (and proliferation of other resistant microorganisms)

### Vascular disorders
- Hypotension

### General disorders and administration site conditions
- Asthenia
- Pain (including pain in back, chest, and extremities)

### Immune system disorders
- Anaphylactic shock (see section 4.4). Anaphylactic and anaphylactoid reactions may sometimes occur even after the first
- Hypersensitivity (see section 4.4)

### Hepatobiliary disorders
- Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
- Blood bilirubin increased
- Hepatitis
- Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (see section 4.4).

### Psychiatric disorders
- Insomnia, nervousness
- Psychotic disorder, depression, confusional state, agitation, anxiety
- Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucinations

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 supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.

No specific antidote exists.

### 5 PHARMACOLOGICAL PROPERTIES
#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antinfectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones

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

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

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (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 classed of antibacterial agents.

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

<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><em>Pseudomonas</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></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><em>H. influenzae</em></td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Non-species related breakpoints(^3)</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
</tbody>
</table>

\(^1\)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.

\(^2\)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.

\(^3\)Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where susceptibility testing is not recommended or for which there is insufficient evidence that the species in question is a good target (*Enterococcus*, *Neisseria*, Gram negative anaerobes)

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 %. 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.

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

<table>
<thead>
<tr>
<th>Cl₁ [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>
</tbody>
</table>
**5.3 Preclinical safety data**

**Acute toxicity**

The median lethal dose (LD$_{50}$) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg. Administration of 500 mg/kg p.o. to monkeys induced little effect apart from vomiting.

**Repeated dose toxicity**

Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg/kg/day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey.

Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The NOELs in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively.

Toxicity after oral dosing in the monkey was minimal with reduced body weight at 100 mg/kg/day together with salivation, diarrhoea and decreased urinary pH in some animals at this dose. No toxicity was seen in the 6-month study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

The NOELs in the six-month studies were concluded to be 20 and 62.5 mg/kg/day in the rat and monkey respectively.

**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 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 oral and intravenous 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

*Tablet core:* Microcrystalline cellulose, Hydroxypropylcellulose, Crospovidone, Magnesium stearate.

*Film coating:* Hypromellose, FD&C blue #2/Indigo carmine aluminum lake (E132), FD&C yellow #6/Sunset Yellow aluminum lake (E110), Iron oxide red (E172), Macrogol 4000, Titanium dioxide (E171).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container
Transparent PVC/PE/PVDC/Aluminium blister in a carton box.
Pack sizes for Evoxil 250mg: Packs of 1, 3, 5, 7 or 10 tablets.
Pack sizes for Prixoter/Lovacin/Voflan 250mg: 1, 5, 7 or 10 tablets.
Pack Sizes for Xavel 250mg: 1, 5 or 10 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
A score line allows adaptation of the dose in patients with impaired renal function.
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 17277/0033, 36, 39, 42 and 70

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2010

10 DATE OF REVISION OF THE TEXT
12/03/2010
1 NAME OF THE MEDICINAL PRODUCT
Evoxil/Lovacin/Prixoter/Voflan/Xavel 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains levofloxacin hemihydrates equivalent to 500 mg of levofloxacin.
Excipients:
Each tablet contains the excipient FD&C yellow #6/Sunset Yellow aluminum lake.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Orange, oblong, biconvex film-coated tablet with a scoreline.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults with infections of mild or moderate severity, Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

- Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),

- Uncomplicated urinary tract infections

- Complicated urinary tract infections (including pyelonephritis)

- Chronic bacterial prostatitis.

- Skin and soft tissue infections.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets are administered once or twice daily.
The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

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

Method of administration
Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals.
Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets should be taken at least two hours before iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

Dosage in patients with normal renal function (creatinine clearance > 50 ml/min)
PER Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets

<table>
<thead>
<tr>
<th>Indication</th>
<th>Daily dose regimen (depending on severity)</th>
<th>Duration of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial sinusitis</td>
<td>500 mg once daily</td>
<td>10 - 14 days</td>
</tr>
<tr>
<td>Acute bacterial exacerbations of chronic bronchitis</td>
<td>250 to 500 mg once daily</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>500 mg once or twice daily</td>
<td>7 - 14 days</td>
</tr>
<tr>
<td>Uncomplicated urinary tract infections</td>
<td>250 mg once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Complicated urinary tract infections including pyelonephritis</td>
<td>250 mg once daily</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>500 mg once daily</td>
<td>28 days</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>250 mg once daily or 500 mg once or twice daily</td>
<td>7 - 14 days</td>
</tr>
</tbody>
</table>

**Special populations**

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

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>500 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>500 mg/12 h</td>
</tr>
<tr>
<td>first dose: 250 mg</td>
<td>first dose: 500 mg</td>
</tr>
<tr>
<td>then: 125 mg/24h</td>
<td>then: 250 mg/24h</td>
</tr>
<tr>
<td>then: 250 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>50-20 ml/min</td>
<td></td>
</tr>
<tr>
<td>19-10 ml/min</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 ml/min (including haemodialysis and CAPD)¹</td>
<td></td>
</tr>
<tr>
<td>then: 125 mg/48h</td>
<td>then: 125 mg/24h</td>
</tr>
<tr>
<td>then: 125 mg/12 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).

**In children**

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

**4.3 Contraindications**

Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets must not be used:
- in patients hypersensitive to levofloxacin, other quinolones or any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents (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 levofloxacin may not be the optimal therapy. Nosocomial infections due to *P. aeruginosa* may require combination therapy.

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).

In infections suspicious for MRSA levofloxacin should be combined with an agent approved to treat MRSA infections.

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/Lovacin/Prixoter/Voflan/Xavel tablets, may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets 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 system 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 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.

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., glivenclamide) 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 or 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 Evoxil/Lovacin/Prixoter/Voflan/Xavel in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly (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, 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 the colouring agent sunset yellow (E110), which may cause allergic reactions.

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**

- **Iron salts, magnesium- or aluminium-containing antacids**
Levofloxacin absorption is significantly reduced when iron salts, buffered formulations or magnesium- or aluminium-containing antacids are administered concomitantly. It is recommended that preparations containing divalent or trivalent cations such as iron salts, buffered formulations or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after Evoxil/Lovacin/Prixoter/Voflan/Xavel tablet administration. No interaction was found with calcium carbonate.

- **Sucralfate**
The bioavailability of Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration (see section 4.2).

- **Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs**
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

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

Other forms of interactions
Meals
There is no clinically relevant interaction with food. Evoxil/Lovacin/Prixoter/Voflan/Xavel tablets may therefore be administered regardless of food intake.

4.6 Pregnancy and lactation
Pregnancy
The product is contraindicated during 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 section 4.3 and 5.3).

Lactation
The product is contraindicated in breast-feeding women. 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 are described according to the MedDRA system organ class below. Frequencies are defined using the following convention:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1000, <1/100)
Rare (≥1/10000, <1/1000)
Very rare (<1/10000)
Not known (cannot be estimated from the available data).

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

Cardiac disorders
<table>
<thead>
<tr>
<th>Category</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
<td>Tachycardia</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Electrocardiogram QT prolonged (see section 4.4 QT interval prolongation and section 4.9)</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Leukopenia, eosinophilia</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td><strong>Not Known</strong></td>
<td>Pancytopenia, haemolytic anaemia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Convulsion, tremor, paraesthesia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Visual disturbance</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Hearing impaired</td>
</tr>
<tr>
<td><strong>Not Known</strong></td>
<td>Tinnitus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Bronchospasm, dyspnoea</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Pneumonitis allergic</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Diarrhoea, nausea</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Vomiting, abdominal pain, dyspepsia, flatulence, constipation</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Diarrhoea-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><strong>Uncommon</strong></td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td><strong>Very rare</strong></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><strong>Uncommon</strong></td>
<td>Rash, pruritus</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Urticaria</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Angioneurotic oedema, photosensitivity reaction</td>
</tr>
<tr>
<td><strong>Not Known</strong></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><strong>Rare</strong></td>
<td>Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia</td>
</tr>
<tr>
<td><strong>Very rare</strong></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><strong>Not Known</strong></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Anorexia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Hypoglycaemia, particularly in diabetic patients (see section 4.4)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Fungal infection (and proliferation of other resistant microorganisms)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Hypotension</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Asthenia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Pyrexia</td>
</tr>
<tr>
<td><strong>Not Known</strong></td>
<td>Pain (including pain in back, chest, and extremities)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic shock (see section 4.4). Anaphylactic and anaphylactoid reactions may sometimes occur even after the first</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity (see section 4.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Insomnia, nervousness</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Psychotic disorder, depression, confusional state, agitation, anxiety</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Psychotic reactions with self-endangering 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 Levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.

No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antinfectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones
ATC code: J01MA12
Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

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

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (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 classed of antibacterial agents.

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

**EUCAST clinical MIC breakpoints for levofloxacin (2009-04-07):**

<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><em>Pseudomonas</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S.pneumoniae</em></td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Streptococcus</em> A, B, C, G</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Non-species related</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>break points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1The 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.

2Strains 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.

3Non-species related breakpoints have been determined mainly on the basis of
pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species.
They are for use only for species that have not been given a species-specific breakpoint and are not for
use with species where susceptibility testing is not recommended or for which there is unsufficient
evidence that the species in question is a good target (*Enterococcus, Neisseria, Gram negative
anaerobes)*

**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 multocid*

*Proteus vulgaris*

*Providencia rettgeri*

**Anaerobic bacteria**

*Peptostreptococcus*

**Other**

*Chlamyphila pneumoniae* *

*Chlamyphila psittaci*
**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%. 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.

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

<table>
<thead>
<tr>
<th>Clr [ml/min]</th>
<th>&lt; 20</th>
<th>20 - 40</th>
<th>50 - 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clk [ml/min]</td>
<td>13</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>t½ [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 (LD₅₀) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg. Administration of 500 mg/kg p.o. to monkeys induced little effect apart from vomiting.

**Repeated dose toxicity**
Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg/kg/day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey.

Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters.
The No Observed Adverse Effect Levels (NOELs) in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively.

Toxicity after oral dosing in the monkey was minimal with reduced body weight at 100 mg/kg/day together with salivation, diarrhoea and decreased urinary pH in some animals at this dose. No toxicity was seen in the 6-month study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

The NOELs in the six-month studies were concluded to be 20 and 62.5 mg/kg/day in the rat and monkey respectively.

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 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 oral and intravenous 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
Tablet core: Microcrystalline cellulose, Hydroxypropylcellulose, Crospovidone, Magnesium stearate.

Film coating: Hypromellose, FD&C blue #2/Indigo carmine aluminum lake (E132), FD&C yellow #6/Sunset Yellow aluminum lake (E110), Iron oxide red (E172), Macrogol 4000, Titanium dioxide (E171), Iron Oxide Yellow

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Keep the blister in the outer carton in order to protect from light.
6.5 Nature and contents of container
Transparent PVC/PE/PVDC/Aluminium blister in a carton box.
Pack sizes: Packs of 1, 5, 7 or 10 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
A score line allows adaptation of the dose in patients with impaired renal function.
Any unused product or waste material should be disposed of in accordance with local requirements.
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 250mg and 500mg film-coated Tablets. Other PILs are available for Lovacin, Prixoter, Voflan and Xavel 250mg and 500mg film-coated Tablets.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Evoxil 250 mg film – coated tablets
Evoxil 500 mg film – coated tablets

Levofloxacin

Read all of this leaflet carefully before you start taking 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 take Evoxil
3. How to take Evoxil
4. Possible side effects
5. How to store Evoxil
6. Further information

1. WHAT EVOXIL TABLETS IS AND WHAT IT IS USED FOR

What this medicine is
The active substance in your tablets is levofloxacin. This belongs to a group of medicines known as fluoroquinolone antibiotics, which kill bacteria.

What this medicine does
Evoxil tablets are 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:
- Sinuses
- 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 TAKE EVOXIL TABLETS

Do not use Evoxil tablets
- 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. tendonitis) relating to treatment with an active substance that belongs to the same class of antibiotics (i.e. fluoroquinolones).
• if you are or planning to become pregnant or if you are breast-feeding.
• if the tablets have been prescribed to children or growing teenagers. They could harm the cartilage of their growing bones. **The tablets are only intended for adults.**

Tell your doctor if you have had any problems with taking medicines in the past.

**Take special care with Evoxil tablets**

• 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 whilst 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 the corticosteroids (cortisone or similar medicines used as anti-inflammatory in many disorders such as asthma, allergic conditions/reactions and arthritis). If you experience any tendon complaints whilst or shortly after taking the tablets you should seek medical advice immediately and rest the affected limb to avoid tendon damage. Do not take the next dose of Evoxil unless your doctor tells you to.
• if you have severe, persistent and/or bloody diarrhoea during or after treatment with the tablets. 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 a 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:
iron salts (used to treat anaemia), magnesium- or aluminium – containing antacids (medicines against heartburn and stomach pain) or medicines containing respective salts. These drugs can reduce the absorption and efficacy of Evoxil tablets and as such they should be taken at least 2 hours before or after Evoxil tablets.

- sucralfate (used to protect the stomach wall). It may affect the absorption and reduce the efficacy of Evoxil tablets. It is best to take sucralfate 2 hours after Evoxil tablets.

- Vitamin K antagonists such as warfarin. In combination with Evoxil tablets 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.

- ciclosporin (e.g. used to treat psoriasis, dermatitis, rheumatism). The effect of this medicine may be prolonged if used in combination with Evoxil tablets.

- 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 tablets.

- 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 infectons (‘macrolide’ antibiotics such as erythromycin, azithromycin and clarithromycin).

**Taking Evoxil tablets with food and drink**

Evoxil tablets may be taken during meals or at any time between meals. Swallow the tablets with a glass of water.

**Pregnancy and Breast-feeding**

Do not take Evoxil tablets if you are pregnant or breast feeding a baby. It could harm your baby.

**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 Evoxil tablets**

This medicinal product contains the colouring agent sunset yellow (E110), which may cause allergic reactions.

### 3. HOW TO TAKE EVOXIL TABLETS

Always take Evoxil exactly as your doctor has told you.

You should check with your doctor or your pharmacist if you are not sure.

The duration of the treatment depends on the type and severity of your infection.

Your doctor will tell you how many tablets to take, at what time and for how long.

Most people need a dose of one or two tablets per day. Patients with reduced kidney activity may need lower doses.

**Taking this medicine**

- Take this medicine by mouth
- Swallow the tablets whole with a glass of water
- The tablets may be taken during meals or at any time between meals
Protect your skin from sunlight

Keep out of direct sunlight while taking this medicine. This is because your skin will become much more sensitive to the sun and may burn, tingle or severely blister if you do not take the following precautions:
• Make sure you use high factor sun creams
• Always wear a hat and clothes which cover your arm and legs.
• Avoid sun beds.

If you are already taking iron tablets, antacids or sulcrafate
• Do not take this medicines at the same time as Levofloxacin film-coated tablets. Take your dose of these medicines at least 2 hours before or after Levofloxacin film-coated tablets.

How much to take
• Your doctor will decide on how many Levofloxacin film-coated tablets you should take.
• The dose will depend on the type of infection you have and where the infection is in your body.
• The length of your treatment will depend on how serious your infection is
• If you feel the effect of your medicine is too weak or strong, do not change the dose yourself, but ask your doctor.

Adults and the elderly.
Infections of sinuses
• Two tablets of Levofloxacin 250 mg, twice a day.
• Or, one tablet of Levofloxacin 500 mg, once each day.

Infection of the lungs, in people with long term breathing problems.
• One or two tablets of Levofloxacin 250 mg, once each day
• Or, ½ tablet or one tablet Levofloxacin 500 mg, once each day

Pneumonia
• Two tablets of Levofloxacin 250 mg, once or twice each day
• Or, one tablet of Levofloxacin 500 mg, once or twice each day.

Infection of the urinary track, including your kidneys or bladder.
• One tablet of Levofloxacin 250 mg, each day
• Or, ½ tablet of Levofloxacin 500 mg, each day

Infection of the prostate gland, where you have a long lasting infection
• Two tablets of Levofloxacin 250 mg, once each day.
• Or, one tablet of Levofloxacin 500 mg, once each day.

Infection of the skin and underneath the skin, including muscles
• One or two tablets of Levofloxacin 250 mg, once or twice each day
• Or, ½ tablet or one tablet Levofloxacin 500 mg, once or twice each day

Adults with kidney problems
Your doctor may need to give you a lower dose

Children and teenagers
The medicine must not be given to children and teenagers.
PAR Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets

**If you take more Evoxil tablets than you should**
If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor. The consequences of an overdose include central nervous system symptoms such as confusion, dizziness, impairment of consciousness, (convulsive) fits and heart disorder, possibly leading to abnormal heart rhythm. In the event of overdose the treatment is according to symptoms. Levofoxacin is not removed from the body by dialysis. No specific antidote exists.

**If you forget to take Evoxil tablets**
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for you to take your next dose. Then go on as before. Do not take a double dose to make up for a missed dose.

**If you stop taking Evoxil tablets**
It is important to finish your course of tablets as prescribed by your doctor. Do not stop, even if you begin to feel better before you have finished them all. If you stop the tablets too soon your condition may get worse. If you feel you have to stop of a side effect, tell a doctor immediately to get advice before taking the next dose.

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

4. **POSSIBLE SIDE EFFECTS**

Like all other medicines Evoxil 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. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

*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 <Levofoxacin> 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.*

*Other side effects include*

Common affects 1 to 10 users in 100
- Nausea, diarrhoea
- Increase in blood levels of liver enzymes

Uncommon affects 1 to 10 users in 1000
- 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: affects 1 to 10 users in 10,000
- 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 rashes (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
- Feeling like tingling, 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 (tendinitis), joint pain or muscle pain
- Decrease in the number of blood platelets leading to tendency to bruise and bleed easily

Very rare: affects less than 1 user in 10,000
- 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.

Not known frequency cannot be estimated from the available data
- Severe blistering reactions of the skin and mucous membranes (Steven’s Johnson syndrome), toxic epidermal necrolysis (Lyells’ 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.
5. HOW TO STORE EVOXIL TABLETS

Keep out of the reach and sight of children.
Do not use this medicine after the expiry date which is shown on the packaging. The expiry date refers to the last day of the month.
Keep the blister in the outer carton in order to protect from light.
Medicines should not be disposed of via wastewater of household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Evoxil contains
Evoxil tablets are available in two strengths: 250 mg and 500 mg. The active substance is levofloxacin.

Each Evoxil 250 mg tablet contains levofloxacin hemihydrates equivalent to 250 mg of levofloxacin

Each Evoxil 500 mg tablet contains levofloxacin hemihydrates equivalent to 500 mg of levofloxacin

The other ingredients are:
Tablet core: Microcrystalline cellulose, hydroxypropylcellulose, crospovidone, magnesium stearate.
Film coating: Hypromellose, FD&C blue #2/Indigo carmine aluminum lake (E132), FD&C yellow #6/Sunset Yellow aluminum lake (E110), iron oxide red (E172), macrogol 4000, titanium dioxide (E171). Additionally the 500 mg tablets contain iron oxide yellow.

What Evoxil looks like and contents of the pack
Evoxil 250 mg film-coated tablets are pink, oblong, biconvex tablets with a scoreline. The tablet can be divided into equal halves.
Evoxil 500 mg film-coated tablets are orange, oblong, biconvex, tablets with a scoreline. The tablet can be divided into equal halves.
Evoxil 250 mg film-coated tablets are packed in blister strips, and are available in pack sizes of 1, 3, 5, 7 and 10 tablets.
Evoxil 500 mg film-coated tablets are packed in blister strips, and are available in pack sizes of 1, 5, 7 and 10 tablets.

Not all pack sizes may be marketed.

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

This medicinal product is authorised in the Member States of the EEA under the following names:

UK/H/1477/01-02/DC
United Kingdom  Evoxil 250 500 mg film-coated tablets
Cyprus    LEVOXACIN
Greece    Evoxil
Germany    Levofloxacin Q-GENERICS 250 500 mg
Italy    CHF 5932

For any information about this medicinal product, please contact the Marketing Authorisation Holder, details provided above.

This leaflet was last approved in...MM/YYYY
Module 4
Labelling

The labelling below is the label 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 250mg film-coated Tablets. Other label texts are available for Evoxil 500mg, Lovacin, Prixoter, Voflan and Xavel 250mg and 500mg film-coated Tablets.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
|---|---|
| Box |

| 1. NAME OF THE MEDICINAL PRODUCT |
|---|---|
| Evoxil 250 mg film-coated tablets |
| Levofloxacin |

| 2. STATEMENT OF ACTIVE SUBSTANCE |
|---|---|
| Each tablet contains levofloxacin hemihydrates equivalent to 250 mg levofloxacin |

| 3. LIST OF EXCIPIENTS |
|---|---|
| Contains E 110. See leaflet for further information. |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
|---|---|
| Film-coated tablet |
| 1 tablet |
| 3 tablets |
| 5 tablets |
| 7 tablets |
| 10 tablets |

| 5. METHOD AND ROUTE OF ADMINISTRATION |
|---|---|
| For oral use |
| 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 |
|---|---|

| 8. EXPIRY DATE |
|---|---|
| EXP: {MM/YYYY} |

| 9. SPECIAL STORAGE CONDITIONS |
|---|---|
| Keep the blister 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 |
|---|---|
PAR Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets

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

12. MARKETING AUTHORISATION NUMBER

PL 17277/0033

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by a doctor

16. INFORMATION IN BRAILLE

Evoxil 250 mg tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Evoxil 250 mg film-coated tablets
Levofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

LOT:

5. OTHER
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Cyprus, Germany, Greece, Italy and the UK considered that the applications for Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets could be approved. These products are prescription only medicines (POM) and are indicated in adults for the treatment of of the following infections when due to levofoxacin-susceptible microorganisms:

• Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

• Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

• Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),

• Uncomplicated urinary tract infections

• Complicated urinary tract infections (including pyelonephritis)

• Chronic bacterial prostatitis.

• Skin and soft tissue infections.

These applications for Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Tavanic 250mg and 500mg film-coated Tablets, the reference product being Tavanic 250mg film-coated Tablets, 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 with the exception of the bioequivalence study 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 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/Xavel 250mg and 500mg film-coated Tablets</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>250mg and 500mg film-coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1477, 81, 79, 83, 2198/001-2/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 17277/0033-4, 36-7, 39-40, 42-3, 70-1</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: \((-\)-(\text{s})-\text{-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.\)}

Structural formula:

![](image)

Molecular formula: \(C_{18}H_{20}FN_{3}O_{4}\cdot\frac{1}{2}H_{2}O\)

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 in the tablet core consist of microcrystalline cellulose, hydroxypropylcellulose, crospovidone, magnesium stearate.

The tablet film-coating for the 250mg film-coated Tablets consists of pharmaceutical excipients hypromellose, FD&C blue #2/Indigo carmine aluminum lake (E132), FD&C yellow #6/Sunset Yellow aluminum lake (E110), iron oxide red (E172), macrogol 4000, titanium dioxide (E171).

The tablet film-coating for the 500mg film-coated Tablets also contains iron oxide yellow.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificate of Suitability for TSE is required.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Tavanic 250mg and 500mg film-coated Tablets.

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 products.

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 of each strength have been provided. The applicant has committed to perform process validation on three production-scale batches of each strength.

Finished Product Specification
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in blisters composed of polyvinylchloride, polyethylene, polyvinylidene chloride and aluminium which are then packed in a carton box. The pack sizes for the 250mg products are as follows:
PAR Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets

Evoxil 250mg: 1, 3, 5, 7 or 10 tablets.
Prixoter/Lovacin/Voflan 250mg: 1, 5, 7 or 10 tablets.
Xavel 250mg: 1, 5 or 10 tablets.

The 500mg product comes in pack sizes of 1, 5, 7 or 10 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 4 years with storage instructions, ‘Keep the blister in the outer carton in order to protect from light’.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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 they contain.

**MAA forms**
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**
It is recommended that Marketing Authorisations are granted for these applications.
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
To support these applications, the Marketing Authorisation Holder has submitted a single dose bioequivalence study:

Study 1
An open-label, single-dose, randomised, two-treatment, two-period, cross-over bioequivalence study of Levofloxacin 500mg Tablets versus Tavanic 500mg Tablets in healthy subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed pre-dose, at baseline and up to 36 hours post dose in each treatment period. The washout period between phases was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (μg/ml/h)</th>
<th>AUC_{0-∞} (μg/ml/h)</th>
<th>C_{max} (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>39.003</td>
<td>40.855</td>
<td>4.865</td>
</tr>
<tr>
<td>Reference</td>
<td>38.797</td>
<td>40.744</td>
<td>4.900</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>100.33 (98.23 – 102.46)</td>
<td>100.07 (98.00 – 102.19)</td>
<td>98.95 (92.55 – 105.79)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for Levofloxacin lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As the 500mg strength products meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to Levofloxacin 250mg Tablets.

3. Post marketing experience
Levofloxacin has a well-recognised efficacy and an acceptable level of safety in the indications approved for Solian Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the Marketing Authorisation is supported.

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

5. Conclusions
The grant of Marketing Authorisations for Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets 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 an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Evoxil/Lovacin/Prixoter/Voflan/Xavel 250mg and 500mg film-coated Tablets and the originator products.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with levofloxacin is considered to have demonstrated the therapeutic value of the compound. 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>
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