Public Assessment Report

Decentralised Procedure

Levofloxacin 250 mg Film-Coated Tablets
Levofloxacin 500 mg Film-Coated Tablets

UK/H/3344/001-2/DC

UK licence no: PL 34771/0014-15

Macleods Pharma UK Limited
LAY SUMMARY

On 27 February 2012, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Macleods Pharma UK Limited Marketing Authorisations (licences) for the medicinal products Levofloxacin 250 mg and 500 mg Film-Coated Tablets (PL 34771/0014-15). These licences were granted via the decentralised procedure (UK/H/3344/001-2/DC). These medicines are only available on prescription from your doctor.

Levofloxacin tablets contain the active ingredient, levofloxacin hemihydrate. Levofloxacin is an antibiotic which is used to treat bacterial infections of the:

- sinuses,
- lungs e.g pneumonia
- kidneys, bladder and urinary tract
- prostrate gland
- skin and soft tissues (including fat and muscle)

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Levofloxacin 250 mg and 500 mg Film-Coated Tablets outweighs the risks and Marketing Authorisations were granted.
# TABLE OF CONTENTS

| Module 1: Information about initial procedure | Page 4 |
| Module 2: Summary of Product Characteristics | Page 5 |
| Module 3: Product Information Leaflets | Page 18 |
| Module 4: Labelling | Page 21 |
| Module 5: Scientific Discussion | Page 25 |
| I Introduction | Page 25 |
| II About the product | Page 27 |
| III.1 Quality aspects | Page 28 |
| III.2 Non-clinical aspects | Page 31 |
| III.3 Clinical aspects | Page 31 |
| IV Overall Conclusion and Benefit:Risk Assessment | Page 35 |
| Module 6 | Steps taken after initial procedure | Page 36 |
# Module 1

| **Product Name** | Levofloxacin 250 mg film-coated tablets  
Levofloxacin 500 mg film-coated tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic Application, 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>250 and 500 mg</td>
</tr>
</tbody>
</table>
| **Marketing Authorisation Holder** | Macleods Pharma UK Limited  
Crewe Hall, Crewe,  
Cheshire, CWI 6UL,  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Germany, Hungary, Italy, Poland, Romania and Spain |
| **Procedure Number** | UK/H/3344/001-2/DC |
| **End of Procedure** | 2 February 2012 |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPCs) for Levofloxacin 250 mg and 500 mg Film-Coated Tablets (PL 34771/0014-15) are as follows: Differences between the two are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Levofloxacin 250 mg film-coated tablets
Levofloxacin 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains
250 mg of levofloxacin as active substance corresponding to 256.23 mg of levofloxacin hemihydrate.

500 mg of levofloxacin as active substance corresponding to 512.46 mg of levofloxacin hemihydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Levofloxacin 250 mg film-coated tablets
Pink colored, capsule shaped, biconvex, film coated tablets, debossed ‘ML’ and ‘62’ on either side of a deep scoreline and a scoreline on other side.

Levofloxacin 500 mg film-coated tablets
Peach colored, capsule shaped, biconvex, film coated tablets, debossed ‘ML’ and ‘63’ on either side of a deep scoreline and a scoreline on other side.

The tablet can be divided into equal parts.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults with infections of mild or moderate severity, Levofloxacin tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms (see section 5.1):

• 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.

Before prescribing Levofloxacin tablets, consideration should be given to official guidance on the appropriate use of antibacterial agents.
4.2 **Posology and method of administration**

Levofloxacin 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.

**Duration of treatment**

The duration of treatment varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin 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**

Levofloxacin 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. Levofloxacin tablets should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

**Posology**

The following dose recommendations can be given for Levofloxacin tablets:

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Daily dose regimen (according to severity)</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute sinusitis</td>
<td>500 mg once daily</td>
<td>10 - 14 days</td>
</tr>
<tr>
<td>Acute 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 prostatitis</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 ≤ 50 ml/min)

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

**In children**

Levofloxacin tablets is contraindicated in children and growing adolescents (less than 18 years of age) (see section 4.3).
4.3 Contraindications
Levofloxacin tablets must not be used:

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

*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 tablets. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin tablets must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

*Clostridium difficile-associated disease*
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin tablets, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Levofloxacin 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 tablets are 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 lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with levofloxacin should be discontinued.

*Patients with G-6- phosphate dehydrogenase deficiency*
Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution.

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

*Hypersensitivity reactions*
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.
Hypoglycemia
As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended. (See section 4.8).

Prevention of photosensitization
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitization.

Patients treated with Vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with Levofloxacin tablets 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. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
  (See sections 4.2, 4.5, 4.8 and 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 method.

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.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Levofloxacin tablets

Iron salts, magnesium- or aluminium-containing antacids
Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids are administered concomitantly with tablets. It is recommended that preparations containing divalent or trivalent cations such as iron salts, or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after Levofloxacin tablets administration (see section 4.2). No interaction was found with calcium carbonate.

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

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

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

Ciclosporin

The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin. In cases of co-administration of these drugs the serum cyclosporine concentration should be monitored.

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).

**Other forms of interactions**

**Meals**

There is no clinically relevant interaction with food. Levofloxacin tablets may therefore be administered regardless of food intake.

**4.6 Fertility, pregnancy and lactation**

**Fertility**

*In non-clinical studies, levofloxacin had no effect on fertility (see section 5.3). It is unknown whether levofloxacin has an effect on fertility in humans.*

**Pregnancy**

There are no data with respect to the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed; thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / fetus (see section 5.3). The product is therefore contraindicated during pregnancy (see section 4.3).

**Lactation**

There is insufficient information with respect to the excretion of levofloxacin in human and/or animal milk. In the absence of these data and given the potential risk of articular damage, levofloxacin is contraindicated during breast-feeding (see section 4.3).

**4.7 Effects on ability to drive and use machines**

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

**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, ≤1/10000), 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.

**Infections and infestations**

Uncommon: Fungal infection (and proliferation of other resistant microorganisms)

**Blood and lymphatic system disorders**

Uncommon: Leukopenia, eosinophilia

Rare: Thrombocytopenia, neutropenia

Very rare: Agranulocytosis

Not Known: Pancytopenia, haemolytic anaemia

**Immune system disorders**

Very rare: Anaphylactic shock (see section 4.4)
Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
Not known: Hypersensitivity (see section 4.4)

Metabolism and nutrition disorders
Uncommon: Anorexia
Very rare: Hypoglycemia, particularly in diabetic patients (see section 4.4)

Psychiatric disorders
Uncommon: Insomnia, nervousness
Rare: Psychotic disorder, Depression, confusional state, agitation, anxiety
Very rare: Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucination

Nervous system disorders
Uncommon: Dizziness, headache, somnolence
Rare: Convulsion, tremor, paraesthesia,
Very rare: sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

Eye disorders
Very rare: Visual disturbance

Ear and Labyrinth disorders
Uncommon: Vertigo
Very rare: Hearing impaired
Not known: Tinnitus

Cardiac disorders
Rare: Tachycardia
Not known: Electrocardiogram QT prolonged (see sections 4.4 and 4.9)

Vascular disorders
Common: Phlebitis
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm, dyspnoea
Very rare: Pneumonitis allergic

Gastrointestinal disorders
Common: Diarrhoea, nausea
Uncommon: Vomiting, abdominal pain, dyspepsia, flatulence, constipation
Rare: Diarrhoea–haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis.

Hepatobiliary disorders
Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon: Blood bilirubin increased
Very rare: Hepatitis
Not known: 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).

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus
Rare: Urticaria
Very rare: Angioneurotic oedema, photosensitivity reaction
Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis
Mucocutaneous reactions may sometimes occur even after the first dose
Musculoskeletal and Connective tissue disorders
Rare: Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia
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
Not Known: Rhabdomyolysis

Renal and urinary disorders
Uncommon: Blood creatinine increased
Very rare: Renal failure acute (e.g. due to nephritis interstitial)

General disorders and administration site conditions
Uncommon: Asthenia
Very rare: Pyrexia
Not known: Pain (including pain in back, chest, and extremities)
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 tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

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: 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 (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance
The main mechanism of resistance is due to a gyr-A mutation. In vitro there is a cross-resistance between levofloxacin and other fluoroquinolones.
Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.
Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from 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>Enterobacteriaceae</td>
<td>≤ 1 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>≤ 1 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>≤ 1 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>≤ 1 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>≤ 2 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>Streptococcus A,B,C,G</td>
<td>≤ 1 mg/L</td>
<td>&gt; 2 mg/L</td>
</tr>
<tr>
<td>H. influenzae M. catarrhalis</td>
<td>≤ 1 mg/L</td>
<td>&gt; 1 mg/L</td>
</tr>
<tr>
<td>Non-species related breakpoints</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 species

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

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

Anaerobic bacteria
Peptostreptococcus
Other
Chlamydia pneumoniae *
Chlamydia 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 coagulase spp

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 thetaiotamicron$
Bacteroides vulgatus$
Clostridium difficile$

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
$ natural intermediate susceptibility

Other information

Nosocomial infections due to P. aeruginosa may require combination therapy

5.2 Pharmacokinetic properties

General pharmacokinetics

Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1h. The absolute bioavailability is approximately 100%. Food has little effect on the absorption of levofloxacin.

Distribution
Approximately 30 - 40% of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

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 8.7μg/g, 8.2 μg/g and 2.0 μg/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

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

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

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

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

**Linearity**
Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

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

<table>
<thead>
<tr>
<th>Clc [ml/min]</th>
<th>&lt; 20</th>
<th>20 - 40</th>
<th>50 - 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cln [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 subjects**
There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

**Gender differences**
Separate analysis for male and female subjects 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
During repeat dose studies, common observations included reduced food consumption and minor alterations in haematological and biochemical parameters at 200 mg/kg/day in the rat and reduced body weight, salivation, diarrhoea and decreased urinary pH at 100 mg/kg/day in the monkey. Levofloxacin had no effect on fertility or reproductive performance and was not teratogenic in the rat. In the rabbit, levofloxacin had no effect on fertility, was not teratogenic and its only effect on fetuses was delayed maturation at doses resulting in maternal toxicity. Levofloxacin induced chromosome aberrations in Chinese hamster lung cells in vitro at or above 100 μg/ml. However, levofloxacin did not show any genotoxic potential in a series of other in vitro and in vivo tests and no indication of carcinogenic potential was observed. 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.

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; hence, this adverse effect is of particular concern in the paediatric population. In the juvenile dog, effects on articular cartilage (blister formation, erosion, cleft formation and/or cavitation) were observed following repeated-oral administration for 7 days at 10 mg/kg/day and above and at 40 mg/kg/day in 4-month and 13-month old animals, respectively. In 4-week old rats, repeated oral administration of levofloxacin for 7 days, cartilage toxicity was observed at 300 mg/kg/day and above; however, no abnormalities were observed following repeated intravenous administration for 2 weeks at up to 160 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Microcrystalline Cellulose
Crospovidone (Type A)
Hypromellose (15 cP)
Magnesium stearate

Tablet coating:
Hypromellose (6 cP) (E464)
Titanium dioxide (E171)
Macrogol 400
Iron Oxide Red (E172)
Polysorbate 80 (E433)
Iron Oxide Yellow (E172)- Levofloxacin 500 mg strength only

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Levofloxacin tablets are available in blisters made of clear PVC coated with PVDC – Aluminium containing 5 or 10 Tablets.
One blister strip per carton
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. As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.
7 MARKETING AUTHORISATION HOLDER
Macleods Pharma UK Limited
Golden Gate Lodge,
Crewe Hall
Crewe, Cheshire
CW1 6UL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 34771/0014
PL 34771/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/02/2012

10 DATE OF REVISION OF THE TEXT
Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levofloxacin 250 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 your 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 get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Levofloxacin tablets are and what they are used for
2. Before you take Levofloxacin tablets
3. How to take Levofloxacin tablets
4. Possible side effects
5. How to store Levofloxacin tablets
6. Further information

1. WHAT LEVOFLAXACIN TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Levofloxacin tablets. Levofloxacin tablets contain a medicine called levofloxacin. This belongs to a group of medicines called antibiotics. Levofloxacin is a "quinolone" antibiotic. It works by killing the bacteria that cause infections in your body.

Levofloxacin tablets can be used to treat infections of:
- Urinary tract.
- Lungs, in people with long-term breathing problems or pneumonia.
- Eyes, including conjunctivitis.
- Skin and infected tissue, including muscle. This is sometimes called "soft tissue".

2. BEFORE YOU TAKE LEVOFLAXACIN TABLETS

Do not take this medicine and tell your doctor if:
- You are allergic to levofloxacin, any other quinolone antibiotic such as moxifloxacin, ciprofloxacin or ofloxacin or any of the other ingredients of Levofloxacin tablets. (listed in section 6 below). Signs of an allergic reaction include: rash, swelling or breathing problems, swelling of your lips, face, throat or tongue.
- You have ever had epilepsy.
- You have ever had a problem with your tendons such as tendinitis that was related to treatment with a "quinolone antibiotic". Tendonitis is the inflammation of a tendon that joins your muscle to your skeleton.
- You are a child or a growing teenager (under 18 years old).
- You are pregnant or might become pregnant or your child may be pregnant.
- You are breast-feeding.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Levofloxacin tablets.

Take special care with Levofloxacin tablets:
Check with your doctor or pharmacist before taking your medicine:
- Levofloxacin may, in rare cases, cause tendonitis (pain and swelling or redness around your tendon). Particularly if you are elderly or if you are taking corticosteroids (steroids and similar medicines). If you have any tendon complaints tell your doctor immediately and rest the affected limb to avoid tendon damage. It may be necessary to stop treatment (see "Do not use Levofloxacin tablets")
- If during your treatment or even weeks after treatment has stopped, you get severe diarrhoea, that contains blood or mucus and does not go away, tell your doctor immediately. This could be signs of serious bowel condition (pseudomembranous colitis) and it may be necessary to stop treatment with Levofloxacin and start treating this condition.

The risk of getting fits may be increased if you take this medicine with other drugs such as fenbufen or similar medicines for rheumatic pain and inflammation or with theophylline (a medicine used to treat asthma), (see also "Taking other medicines"). Make sure you doctor knows about your medical history, so he can give you appropriate advice.

Tell your doctor if you have a problem with an enzyme called glucose-6-phosphate dehydrogenase (G6-PD) (a rare hereditary disease). This condition causes a deficiency of certain chemicals in the red blood cells and if you are given Levofloxacin, it may lead to the breakdown of red blood cells resulting in anaemia and an yellowing of the skin (jaundice).
- If you have a kidney problem, your doctor may have to adjust the dose of this medicine (see also section 4 "How to use Levofloxacin tablets").
- Levofloxacin has been known to cause serious allergic reactions, even during or after the first dose. If you develop a rash, difficulty in breathing, or other symptoms of an allergic reaction (see also section 4 "Possible side effects") tell your doctor or pharmacist immediately.
- Tell your doctor or pharmacist if you are diabetic and are taking insulin or hypoglycaemic agent, you may have a hypoglycaemic reaction while on Levofloxacin. Your doctor will carefully monitor your blood glucose level.
- Do not stay out in strong sunlight for unnecessarily long periods and do not use a sun-lamp or solarium while you are taking Levofloxacin. This is because you may become more sensitive to light while taking Levofloxacin tablets (purpura-like reactions).
- Tell your doctor or pharmacist if you are taking a blood thinner such as Warfarin as taking these two medicines together can increase the risk of bleeding problems (see also "Taking other medicines").
- Tell your doctor if you have had a psychiatric disease as you may have thoughts of suicide or of harming yourself when you are on Levofloxacin. If this happens your treatment will be stopped immediately.
- A rare heart problem may occur called prolonged QT interval which causes abnormal heart beat and can be dangerous. This is seen on an electrocardiogram test. The chances of this event are increased if you have a family history of prolonged QT interval, you have low potassium or magnesium levels, you are taking drugs known to prolong the QT interval such as medicines to control heart rhythm, antidepressants or some kind of antibiotics or if you are elderly (see also "Taking other medicines"). Tell your doctor or pharmacist if you have changes in your heart rate or if you feel fainting spells.
- If you experience weakness, tingling or numbness of arms and legs or face tell your doctor or pharmacist immediately as treatment may have to be stopped.
- Levofloxacin may produce false positive urine screening results for opiates (narcotic drugs). Tell your doctor if you are having tests done.
- Levofloxacin has been known to cause effects on the liver which may rarely progress to liver failure mainly in patients with underlying diseases. Contact your doctor right away if you have unexplained symptoms such as loss of appetite, yellowing of your skin or white of your eyes, dark coloured urine, itching or abnormal pain or tenderness.
- Levofloxacin not recommended in known or suspected MRSA infection.

Taking other medicines
Please tell your doctor or Pharmacist if you are taking or have recently taken any other medicine, including medicines that you have obtained without a prescription. It is especially important to mention the following medicines:
- Antacids (medicines against heartburn or stomach pain) that contain magnesium or aluminium and medicines containing iron salts (use to treat anaemia) (see also "How to take Levofloxacin tablets"
- Sucralfate (medicines to protect the stomach wall). (See also "How to take Levofloxacin tablets")
- Fenbufen or similar medicines for rheumatic pain and inflammation, or with theophylline (a medicine used to treat asthma). This is because the risk of getting fits may be increased if you take Levofloxacin with these medicines.
- Prednison (for arthritis) or cortisone (for stomach ulcers and heartburn) because they reduce your kidneys ability to get rid of your medicines.
- Ciclosporin (a medicine to reduce the activity of the immune system after organ transplants for example). Levofloxacin may prolong the effect of this medicine.
- Medicines to thin your blood, such as warfarin.
PAR Levofloxacin 250mg & 500 mg Film-Coated Tablets

UK/H/3344/001-2/DC

- Medicines known to prolong the QT interval: antidepressants such as amitriptyline, antibiotics such as clarithromycin and medicines to control your heart rhythm called class A. (Such as quinidine, procainamide, amiodarone) (see also “Take special care with Levofloxacin tablets”)

Taking Levofloxacin with food and drink
You can take your Levofloxacin tablets with or without food. You should take your tablet with a drink of water.

Pregnancy and breast-feeding
Do not take this medicine if:
- You are pregnant, might become pregnant or think you may be pregnant
- You are breast-feeding or planning to breast-feed

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
You may get side effects after taking this medicine, including feeling dizzy, sleepy, a spinning feeling (vertigo) or changes to your eyesight. Some of these side effects can affect you being able to concentrate and your reaction speed. If this happens, do not drive or carry out any work that requires a high level of attention.

3. HOW TO TAKE LEVOFLAXIN TABLETS

Always take Levofloxacin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Take this medicine by mouth
- Swallow the tablets whole with a drink 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 cream
- Always wear a hat and clothes which cover your arms and legs
- Avoid sun beds

If you are already taking Levofloxacin tablets, take your dose at least 2 hours before or after Levofloxacin tablets

How much to take
- Your doctor will decide on how many Levofloxacin 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 too strong, do not change the dose yourself, but ask your doctor

Adults and the elderly

Sinus
- Two tablets of Levofloxacin tablets, once each day

Lungs, in people with long-term breathing problems
- One or two tablets of Levofloxacin tablets, once each day

Pneumonia
- Two tablets of Levofloxacin tablets, once each time

Urinary tract, including your kidneys or bladder
- One tablet of Levofloxacin tablets, each day

Prostate gland
- Two tablets of Levofloxacin tablets, once each day

Skin and underlying skin, including muscles
- One or two tablets of Levofloxacin tablets, once each day

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

Children and Teenagers
This medicine must not be given to children or teenagers.

If you take more Levofloxacin tablets than you should
If you accidentally take more than you should, tell a doctor or other medical advice straight away. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen: convulsions fits (seizures), feeling confused, dizzy, weakness in heart beats as well as feeling sick (nausea).

If you forget to take Levofloxacin tablets
If you forget to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not double the next dose to make up for the missed dose.

If you stop taking Levofloxacin tablets
Do not stop taking Levofloxacin tablets just because you feel better. It is important that you complete the course of tablets that your doctor has prescribed for you. If you stop taking the tablets too soon, the infection may return, your condition may get worse or the bacteria may become resistant to the medicine.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levofloxacin tablets can cause side effects, although not everybody gets them. These effects are normally mild or moderate and often disappear after a short time.

Stop taking Levofloxacin tablets and see a doctor or go to a hospital straight away, if you notice the following side effect:

Very rare (affects less than 1 person in 10,000)
- You have an allergic reaction. The signs may include: a rash, swelling or breathing problems, swelling of your lips, face, throat, or tongue.

Stop taking Levofloxacin tablets and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

Rare (affects less than 1 person in 1000)
- Watery diarrhoea which may have blood in it, possibly with stomach cramps and a high temperature. The se could be signs of a severe bowel problem
- Pain and inflammation in your tendons. The Achilles tendon is affected most often and in some cases, the tendon could break
- Fits (convulsions)

Very rare (affects less than 1 person in 10,000)
- Burning, tingling, pain or numbness. These may be signs of something called "neuropathy"
- Other:
  - Severe skin rash which may include blistering or peeling of the skin around your eyes, lips, mouth, nose and genitals
  - Loss of appetite, skin and eyes becoming yellow in colour, dark-coloured urine, itching, or tender stomach (abdomen). These may be signs of liver problems

Tell your doctor if any of the following side effects gets serious or lasts longer than a few days:

Common (affects 1 person in 10)
- Feeling sick (nausea) and diarrhoea
- Increase in the level of some liver enzymes in your blood
- Inflammation of vein (phlebitis)

Uncommon (affects less than 1 person in 100)
- Itching and skin rash
PAR Levofloxacin 250mg & 500 mg Film-Coated Tablets

- Loss of appetite, stomach upset or indigestion (dyspepsia), being sick (vomiting) or pain in your stomach area, feeling bloated (distension) or constipation
- Headache, feeling dizzy, a spinning feeling (vertigo), feeling sleepy, sleeping problems or feeling nervous
- Blood tests may show unusual results due to liver or kidney problems
- Changes in the number of white blood cells shown up in the results of some blood tests
- General weakness
- Changes in the number of other bacteria or fungi may increase, which may need to be treated

Rare (affects less than 1 person in 1,000)
- Tingling feeling in your hands and feet (paresthesia) or trembling
- Feeling stressed (anxiety), depressed, mental problems, feeling relieve (apathy) or feeling confused
- Unusual fast beating of your heart or low blood pressure (hypotension)
- Joint pain or muscle pain
- Bruising and bleeding easily due to a lowering in the number of blood platelets
- Low number of white blood cells (caused by neutropenia)
- Difficulty breathing (asthma or bronchial asthma)
- Shortness of breath (dyspnoea)
- Severe itching or itching (called urticaria)
- Bloody diarrhoea, diarrhoea—haemorrhagic

Very rare (affects less than 1 person in 10,000)
- Increased sensitivity of your skin to sun and ultraviolet light
- Lowering of your blood sugar levels (hypoglycaemia). This is important for people that have diabetes
- Problems with your hearing or eyesight or changes in the way things taste or smell
- Seeing or hearing things that are not there (hallucinations), change in your opinion and thoughts (psychotic reactions) with a chance of having suicidal thoughts or actions
- Loss of circulation (paraplegic-like shock)
- Muscle weakness. This is important in people with myasthenia gravis (a rare disease of the nervous system)
- Inflammation of the liver. Changes in the way your kidneys work and occasional kidney failure which may be due to an allergic kidney reaction called interstitial nephritis
- Fever, sore throat and a general feeling of being unwell that does not go away. This may be due to a lowering in the number of white blood cells
- Fever and allergic lung reactions

Other side effects include:
- Lowering in red blood cells (anaemia). This can make the skin pale or yellow due to damage of the red blood cells and lowering in the number of all types of blood cells
- Exaggerated immune response (hypersensitivity)
- Sweating too much (hyperhidrosis)
- Pain, including pain in the back, chest and extremities
- Problems moving and walking
- Attacks of porphyria in people who already have porphyria (a rare metabolic disease)
- Inflammation of your urethra that can cause blood around your body (vessels) due to an allergic reaction
- Heart problems such as abnormal fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called prolongation of QT interval), seen on ECG, electrical activity of the heart

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.

5. HOW TO STORE LEVOFLOXACIN tablets

Keep out of the reach and sight of children.
This medicine does not require any special storage conditions.

Do not use Levofloxacin tablets after the expiry date (EXP) which is stated on the container.
Machinery should not be disposed of via wastewater or 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 Levofloxacin tablets contain

The active ingredient is levofloxacin. Each film-coated tablet contains 250 mg levofloxacin as levofloxacin hydrochloride. The other ingredients are:
- Tablet core: Microcrystalline cellulose (type A), Hypromellose (15 cP), Monohydrate cellulose and Magnesium stearate
- Tablet coating: Hypromellose (6 cP) (E464), Titanium dioxide (E171), Maize gum 400, Iron oxide red (E172), Polysorbates 80 (E438)

What Levofloxacin tablets look like and contents of the pack

Levofloxacin 250 mg film-coated tablets are pink-coated, capsule-shaped, biconvex, film-coated tablets, debossed ‘ML’ and ‘6Z’ on either side of a deep scoreline and ascorbic acid on other side. The tablets can be divided into two equal halves, in case half the tablet dose has been recommended by the physician.
Levofloxacin tablets are provided in blister strip pack having 5 or 10 tablets. One blister strip is supplied per carton.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Macleods Pharma UK Limited
Golden Gate Lodge, Great Western Road, Crewe, Cheshire, CW1 6UL, United Kingdom

Manufacturer
Pepacton Pharmaceuticals Ltd
UK Great Western, Crewe, Cheshire CW1 6UL, United Kingdom.

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

- United Kingdom: Levofloxacin 250 mg Film-coated tablets
- Germany: Levofloxacin Macleods 250 mg Filmtablette
- Hungary: Mclevo 250 mg Filmtabletta
- Italy: Levofloxacin a Macleods 250 mg compresse rivestite onfiilm
- Poland: Levofloxacin Macleods 250 mg tabletki powlekane
- Romania: Levofloxacin a Macleods 250 mg comprimate filmate
- Spain: Levofloxacin Mcleods 250 mg comprimidos recubiertos con pelicula

This leaflet was last revised in 02/2012
PAR Levofloxacin 250mg & 500 mg Film-Coated Tablets

UK/H/3344/001-2/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levofloxacin 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 your 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 Levofloxacin tablets are and what they are used for
2. Before you take Levofloxacin tablets
3. How to take Levofloxacin tablets
4. Possible side effects
5. How to store Levofloxacin tablets
6. Further information

1. WHAT LEVOFLOXACIN TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Levofloxacin tablets. Levofloxacin tablets contain a medicine called Levofloxacin. This belongs to a group of medicines called antibiotics. Levofloxacin is a “quinolone” antibiotic. It works by killing the bacteria that cause infections in your body.

Levofloxacin tablets can be used to treat infections of the:
- Paranasal 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 LEVOFLOXACIN TABLETS

Do not take this medicine and tell your doctor if:
- You are allergic to levofloxacin, any other quinolone antibiotic such as moxifloxacin, grepafloxin or ofloxacin or any of the other ingredients of Levofloxacin tablets (listed in Section 6 below) Signs of an allergic reaction include: a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue
- You have ever had a problem with your tendons such as tendinitis that was related to treatment with a “quinolone antibiotic”. Attention is the cord that joins your muscle to your skeleton
- You are a child or a growing teenager (under 18 years old)
- You are pregnant, might become pregnant or think you may be pregnant
- You are breastfeeding

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Levofloxacin tablets.

Take special care with Levofloxacin tablets:
Check with your doctor or pharmacist before taking this medicine if:
- Levofloxacin may, in rare cases, cause tendons (pain or swelling or tenderness around your tendons. Particularly if you are elderly or if you are taking corticosteroids (cortisone and similar medicines). If you have any tendon complaints tell your doctor immediately and restart the affected limb to avoid tendon damage. It may be necessary to stop treatment (see “Do not use Levofloxacin tablets”)
- If during your treatment or even weeks after treatment has stopped, you get severe diarrhea, that may contain blood or mucus and does not go away, tell your doctor immediately. This could be sign of serious bowel condition (pseudo-membranous colitis) and it may be necessary to stop treatment with Levofloxacin and start treating this condition.
- The risk of getting fits may also be increased if you take this medicines with other drugs such as theophylline or similar medicines for rheumatic pain and inflammation or with theophylline (a medicine used to treat asthma). (see also “Taking other medicines”). Make sure your doctor knows about your medical history, so he can arrange your appropriate advice.
- Tell your doctor if you have a abnormality of an enzyme called glucose-6-phosphate dehydrogenase (G6PD) (a rare hereditary disease). This condition causes a deficiency of certain chemicals in the red blood cells and if you are given Levofloxacin, it may lead to the break down of red blood cells resulting in anaemia and yellowing of the skin (jaundice).
- If you have a kidney problems your doctor may have to adjust the dose of this medicines (see also section 3 “How to use Levofloxacin tablets”)
- Levofloxacin has been known to cause serious allergic reactions, even during or after the first dose. If you develop hives of skin rash, difficulty in breathing, or other symptoms of an allergic reaction (see also section 4 “Possible side effects”) Tell your doctor or pharmacist immediately.
- Tell your doctor or pharmacist if you are diabetic and are taking insulin or hypoglycaemic agent, you may have a hypoglycaemic reaction while on Levofloxacin. Your doctor will carefully monitor your blood glucose level.
- Do not stay out in strong sunlight for unreasonably long periods and do not use a sun-lamp or suntan while you are taking Levofloxacin. This is because you may become more sensitive to light while taking Levofloxacin tablets (sunburn-like reactions).
- Tell your doctor or pharmacist if you are taking a blood thinner such as Warfarin as taking these two medicines together can increase the risk of bleeding problems. (see also “Taking other medicines”)
- Tell your doctor if you buy or have had psychiatric disease, as you may have thoughts of suicide or of harming yourself when you are on Levofloxacin.
- If this happens your treatment will be stopped immediately.
- A rare heart problem may occur called prolonged QT interval which causes abnormal heart beat and can be dangerous. This is seen on an electrocardiogram test. The chances of this event are increased if you have a family history of prolonged QT interval, you have low potassium or magnesium levels, you are taking drugs known to prolong the QT interval such as medicines to control heart rhythm, antidepressant or some kinds of antibiotics or if you are elderly (see also “Taking other medicines”)
- Tell your doctor or pharmacist if you have changes in the way your heartbeat or if you fainting spells.
- If you experience weakness, tingling or numbness of arms and legs or face to your doctor or pharmacist immediately as treatment may have to be stopped.
- Levofloxacin may produce false positive urine screening results for opiates (morphine or codeine). Tell your doctor if you are taking these drugs.
- Levofloxacin may be known to cause effects on the liver which may rarely progress to liver failure mainly in patients with underlying disease. Contact your doctor right away if you have unexplained symptoms such as loss of appetite, yellowing of your skin or white of your eyes, dark coloured urine, itching or abdominal pain or tenderness.
- Levofloxacin not recommended in known or suspected MRI/SAFInfection.

Taking other medicines
Please tell your doctor or Pharmacist if you are taking or have recently taken any other medicines, including medicines that you have obtained without a prescription. It’s especially important to mention the following medicines:
- Antacids (medicines against heartburn or stomach pain) that contain magnesium or aluminium and medicines containing iron salts (use to treat anaemia) (see also “How to take Levofloxacin tablets”)
- Sulfinpyrazone (medicines to protect the stomach wall). (See also “How to take Levofloxacin tablets”)
- Fibrinolytic or similar medicines for rheumatic pain and swelling, or theophylline (a medicine used for respiratory diseases such as asthma). This is because the risk of getting fits may be increased if you take Levofloxacin with these medicines.
- Probenecid (for arthritis) or cimetidine (for stomach ulcer and heartburn) because they reduce your kidneys ability to get rid of your medicines.
- Colchycrin (a medicine to reduce the activity of the immune system after organ transplants for example). Levofloxacin may prolong the effect of this medicines.
- Medicines to thin your blood, such as warfarin.
- Medicines known to prolong the QT interval: antidepressants such as amitriptyline, antibiotics such as clarithromycin and medicines to control your heart rhythm called class A. (Such as quinidine, procainamide, amiodarone) (see also "Take special care with Levofloxacin tablets")

Taking Levofloxacin with food and drink
You can take your Levofloxacin tablets with or without food. You should take your tablet with a drink of water.

Pregnancy and breast-feeding
Do not take this medicine if:
- You are pregnant, might become pregnant or think you may be pregnant
- You are breast-feeding or planning to breast-feed
Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
You may get side effects after taking this medicine, including feeling dizzy, sleepy, a spinning feeling (vertigo) or changes to your eyesight. Some of these side effects can affect you being able to concentrate and your reaction speed. If this happens, do not drive or carry out any work that requires a high level of attention.

3. HOW TO TAKE LEVOFLOXACIN TABLETS

Always take Levofloxacin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Take this medicine by mouth
- Swallow the tablets whole with a drink 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 cream
- Always wear a hat and clothes which cover your arms and legs
- Avoid sun beds

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

How much to take
- Your doctor will decide on how many Levofloxacin 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
- Sinuses
  - One tablet of Levofloxacin tablets, once each day
- Lungs, in people with long-term breathing problems
  - Half tablet or one tablet of Levofloxacin tablets, once each day
- Pneumonia
  - One tablet of Levofloxacin tablets, once or twice each day
- Urinary tract, including your kidneys or bladder
  - Half tablet of Levofloxacin tablets, each day
- Prostate gland
  - One tablet of Levofloxacin tablets, once each day
SKIN AND UNDERNEATH THE SKIN, INCLUDING MUSCLES
• Half tablet or one tablet of Levofloxacin tablets, once or twice each day

ADULTS WITH KIDNEY PROBLEMS
Your doctor may need to give you a lower dose.

CHILDREN AND TEENAGERS
This medicine must not be given to children or teenagers.

IF YOU TAKE MORE LEVOFLOXACIN TABLETS THAN YOU SHOULD
If you accidentally take more tablets than you should, tell a doctor or get other medical advice straight away. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen:
• Convulsive fits (seizures), feeling confused, dizzy, less conscious and heart problems - leading to uneven heartbeats as well as feeling sick (nausea).

IF YOU FORGET TO TAKE LEVOFLOXACIN TABLETS
If you forget to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not double up the next dose to make up for the missed dose.

IF YOU STOP TAKING LEVOFLOXACIN TABLETS
Do not stop taking Levofloxacin tablets just because you feel better. It is important that you complete the course of tablets that your doctor has prescribed for you. If you stop taking the tablets too soon, the infection may return, your condition may get worse or the bacteria may become resistant to the medicines.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Levofloxacin tablets can cause side effects, although not everybody gets them. These effects are normally mild or moderate and often disappear after a short time.

STOP TAKING LEVOFLOXACIN TABLETS AND SEE A DOCTOR OR GO TO A HOSPITAL STRAIGHT AWAY IF YOU NOTICE THE FOLLOWING SIDE EFFECT:
• Very rare (affects less than 1 person in 10,000)
  • You have an allergic reaction. The signs may include: a rash, swelling of your lips, face, throat, or tongue

STOP TAKING LEVOFLOXACIN TABLETS AND SEE A DOCTOR STRAIGHT AWAY IF YOU NOTICE ANY OF THE FOLLOWING SERIOUS SIDE EFFECTS - YOU MAY NEED URGENT MEDICAL TREATMENT:
• Rare (affects less than 1 person in 1000)
  • Watery diarrhoea which may have blood in it, possibly with stomach cramps and a high temperature. These could be signs of a severe bowel problem
  • Pain and inflammation in your tendons. The Achilles tendon is affected most often and in some cases, the tendon could break
  • Fits (convulsions)

• Very rare (affects less than 1 person in 10,000)
  • Burning, tingling, pain or numbness. These may be signs of something called 'neuropathy'

OTHER:
• Severe skin rashes which may include blistering or peeling of the skin around your lips, eyes, mouth, nose and genitals
• Loss of appetite, skin and eyes becoming yellow in colour, dark-coloured urine, itching, or tender stomach (abdomen). These may be signs of liver problems

TELL YOUR DOCTOR IF ANY OF THE FOLLOWING SIDE EFFECTS GETS SERIOUS OR LASTS LONGER THAN A FEW DAYS:
• Common (affects less than 1 person in 10)
  • Feeling sick (nausea) and diarrhoea
  • Increase in the level of some liver enzymes in your blood
  • Inflammation of vein (phlebitis)
- Medicines to thin your blood, such as warfarin.
- Medicines known to prolong the QT interval: antidepressants such as amitriptyline, antibiotics such as clarithromycin and medicines to control your heart rhythm called class A. (Such as quinidine, procainamide, amiodarone) (see also "Take special care with Levofloxacin tablets")

**Taking Levofloxacin with food and drink**

You can take your Levofloxacin tablets with or without food. You should take your tablet with a drink of water.

**Pregnancy and breast-feeding**

Do not take this medicine if:
- You are pregnant, might become pregnant or think you may be pregnant
- You are breast-feeding or planning to breast-feed

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

**Driving and using machines**

You may get side effects after taking this medicine, including feeling dizzy, sleepy, a spinning feeling (vertigo) or changes to your eyesight. Some of these side effects can affect you being able to concentrate and your reaction speed. If this happens, do not drive or carry out any work that requires a high level of attention.

3. **HOW TO TAKE LEVOFLOXACIN TABLETS**

Always take Levofloxacin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Taking this medicine**
- Take this medicine by mouth
- Swallow the tablets whole with a drink 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 cream
- Always wear a hat and clothes which cover your arms and legs
- Avoid sun beds

**If you are already taking iron tablets, antacids or sucralfate**
- Do not take these medicines at the same time as Levofloxacin tablets.
  Take your dose at least 2 hours before or after Levofloxacin tablets

**How much to take**
- Your doctor will decide on how many Levofloxacin 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**

**Sinuses**
- One tablet of Levofloxacin tablets, once each day

**Lungs, in people with long-term breathing problems**
- Half tablet or one tablet of Levofloxacin tablets, once each day

**Pneumonia**
- One tablet of Levofloxacin tablets, once or twice each day

**Urinary tract, including your kidneys or bladder**
- Half tablet of Levofloxacin tablets, each day

**Prostate gland**
- One tablet of Levofloxacin tablets, once each day
Uncommon (affects less than 1 person in 100)
- Itching and skin rash
- Loss of appetite, stomach upset or indigestion (dyspepsia), being sick (vomiting) or pain in your stomach area, feeling bloated (flatulence) or constipation
- Headache, feeling dizzy, a spinning feeling (vertigo), feeling sleepy, sleeping problems or feeling nervous
- Blood tests may show unusual results due to liver or kidney problems
- Changes in the number of white blood cells shown up in the results of some blood tests
- General weakness
- Changes in the number of other bacteria or fungi may increase, which may need to be treated

Rare (affects less than 1 person in 1,000)
- Tingling in your hands and feet (paresthesia) or trembling
- Feeling stressed (anxiety), depressed, mental problems, feeling restless (agitation) or feeling confused
- Unusual fast beating of your heart or low blood pressure (hypotension)
- Joint pain or muscle pain
- Bruising and bleeding easily due to a lowering in the number of blood platelets
- Low number of white blood cells (called neutropenia)
- Difficulty breathing or wheezing (bronchospasm)
- Shortness of breath (cyanosis)
- Severe itching or hives (called urticaria)
- Bloody diarrhoea (diarrhoea-haemorrhagic)

Very rare (affects less than 1 person in 10,000)
- Increased sensitivity of your skin to sun and ultraviolet light
- Lowering of your blood sugar levels (hypoglycaemia). This is important for people that have diabetes
- Problems with your hearing or eyesight or changes in the way they taste and smell
- Seeing or hearing things that are not there (hallucinations), change in your opinion and thoughts (psychotic reactions) with a chance of having suicidal thoughts or actions
- Loss of circulation (anaphylactic like shock)
- Muscle weakness. This is important in people with myasthenia gravis (a rare disease of the nervous system)
- Inflammation of the liver, changes in the way your kidney works and occasional kidney failure which may be due to an allergic kidney reaction called interstitial nephritis
- Fever, sore throat and a general feeling of being unwell that does not go away. This may be due to a lowering in the number of white blood cells
- Fever and allergic lung reactions

Other side effects include:
- Lowering in red blood cells (anaemia). This can make the skin pale or yellow due to damage of the red blood cells and lowering in the number of all types of blood cells
- Exaggerated immune response (hypersensitivity)
- Sweating too much (hyperhidrosis)
- Pain, including pain in the back, chest and extremities
- Problems moving and walking
- Attacks of porphyria in people who already have porphyria (a very rare metabolic disease)
- Inflammation of your tubes that carry blood around your body (vessels) due to an allergic reaction
- Heart problems such as abnormal fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called ‘prolongation of QT interval’, seen on ECG, electrical activity of the heart)

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.

5. HOW TO STORE LEVOFLOXACIN TABLETS
Keep out of the reach and sight of children. This medicine does not require any special storage conditions. Do not use Levofoxacin tablets after the expiry date (EXP) which is stated on the carton and foil. Medicines should not be disposed of via wastewater or 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 Levofoxacin tablets contain
The active ingredient is levofoxacin. Each film-coated tablet contains 500 mg of levofoxacin as levofoxacin hemihydrate. The other ingredients are:
- Tablet core: Crospovidone (type A), Hypromellose (15 cP), Microcrystalline cellulose and Magnesium stearate
- Tablet coating: Hypromellose (6 cP) (E464), Titanium dioxide (E171), Macrogol 400, Polysorbate 80 (E433), Iron oxide yellow (E172), Iron oxide red (E172)

What Levofoxacin tablets look like and contents of the pack
Levofoxacin 500 mg film-coated tablets are peach colored, capsule shaped, biconvex, film-coated tablets, debossed ‘ML’ and ‘53’ on either side of a deep score line and a score line on other side. The tablets can be divided into two equal halves, in case half the tablet dose has been recommended by the physician.
Levofoxacin tablets are provided in blister-pack having 5 or 10 tablets. One blister strip is included per carton. Not all pack sizes may be marketed.

MACLEODS
Marketing Authorisation Holder
Macleods Pharma UK Limited
Golden Gate Lodge, Crowe Hall, Crewe, Cheshire CW1 6UL
United Kingdom

Manufacturer
Paddock Pharmaceuticals Ltd.
UK Crowe Hall, Crewe, Cheshire CW1 6UL, United Kingdom.

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

United Kingdom Levofoxacin 500 mg Film-coated tablets
Germany Levofoxacin Macleods 500 mg Filmtabletten
Hungary Madeyo 500 mg Filmtabletta
Italy Levofloxacina Macleods 500 mg compresse rivestite con film
Poland Levofloxacyna Macleods 500 mg tabletki powlekane
Romania Levofloxacina Macleods 500 mg comprimate filmate
Spain Levofoxacina Macleods 500 mg comprimidos recubiertos con película

This leaflet was last revised in 02/2012
Module 4
Labelling

Carton

Levofloxacin 250 mg
Film-coated Tablets

Each film-coated tablet contains 250 mg of levofloxacin as levofloxacin hemihydrate

Affix Dispensing Label Here

Do not chew.
Read the package leaflet before use.
Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.
PL 3877/2014

Blister foil
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
On 2 February 2012, Germany, Hungary, Italy, Poland, Romania, Spain and the UK agreed to grant Marketing Authorisations (MAs) to Macleods Pharma UK Limited for the medicinal products Levofloxacin 250 mg and 500 mg Film-Coated Tablets. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (UK/H/3344/001-2/DC). After the national phase, licences were granted in the UK on 27 February 2012 (PL 34771/0014-15).

These applications were made under Article 10(1) of Directive 2001/83/EC for Levofloxacin 250 mg and 500 mg Film-Coated Tablets, containing the known active substance, levofloxacin hemihydrate. The reference medicinal products for these applications are Tavanic 250 mg and 500 mg Film-Coated Tablets (PL 13042/0011-12), both licensed on 6 June 1997 to Sanofi-Aventis, UK. The reference products have been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired.

The fluoroquinolones are a group of synthetic, broad-spectrum antibiotics with bactericidal activity. Levofloxacin is a third generation fluoroquinolone, with enhanced activity against Gram-positive organisms, and is the active S-enantiomer of D-ofloxacin. Levofloxacin binds to the A subunit of deoxyribonucleic acid (DNA) gyrase and DNA topoisomerase IV in bacteria, and causes defective supercoiling of DNA and also impairment of relaxation of supercoiling in chromosomes and plasmids. It exhibits high potency in vitro and a long elimination half-life, thus permitting once-daily dosing. Although the rate of resistance to other antibiotic classes has grown, levofloxacin has maintained efficacy with generally very low rates of resistance world-wide.

In adults with infections of mild or moderate severity, levofloxacin tablets have been licensed for the treatment of the following infections when adequately diagnosed:
- Acute sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated urinary tract infections
- Complicated urinary tract infections including pyelonephritis
- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

No new preclinical or clinical studies were conducted for these applications, which is acceptable given that the applications are for generic versions of products that have been licensed for over 10 years. Two bioequivalence studies have been provided to support these applications.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for their manufacture and assembly. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH 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). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active substances is well established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that the marketing of this product will change the overall use pattern of the existing market.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Levofloxacin 250 mg film-coated tablets  
Levofloxacin 500 mg film-coated tablets  
Levofloxacin hemihydrate |
<table>
<thead>
<tr>
<th></th>
<th></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>J01MA12 (Quinolone antibacterials, Fluoroquinolones)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated tablet, 250 and 500 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3344/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany, Hungary, Italy, Poland, Romania and Spain</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 34771/0014-15</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder     | Macleods Pharma UK Limited  
Crewe Hall, Crewe,  
Cheshire, CWI 6UL,  
United Kingdom                                      |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Levofloxacin Hemihydrate

INN: Levofloxacin Hemihydrate
Chemical name:
1.) (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperizinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxacine-6-carboxylic-acid, hemihydrate
2.) (3S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperizinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxacine-6-carboxylic-acid, hydrate(2:1)
3.) (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperizinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxacine-6-carboxylic-acid, hydrate(2:1)

Structure:

![Structure of Levofloxacin Hemihydrate]

Molecular formula: $\text{C}_{18}\text{H}_{20}\text{FN}_{3}\text{O}_{4} \cdot \frac{1}{2} \text{H}_{2}\text{O}$
Molecular weight: 370.38 g/mol

General Properties

Description:
Levofloxacin hemihydrate is a white to yellow crystalline powder

Solubility:
It is freely soluble in glacial acetic acid, soluble in chloroform and dilute acids and slightly soluble in water and ethanol.

Levofloxacin hemihydrate is currently not the subject of a European Pharmacopoeia (Eur Ph.) or British Pharmacopoeia (BP) monograph.

Manufacture

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.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. 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 Certificates of Analysis have been provided for all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated for the drug substance supporting a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**
**Description and Composition**
The proposed product is a film-coated tablet. The product is formulated to contain 250 mg or 500 mg of levofloxacin as active substance corresponding to 256.23 mg or 512.46 mg of levofloxacin hemihydrate respectively with the following description:

**Levofloxacin 250 mg film-coated tablets**
Pink colored, capsule shaped, biconvex, film coated tablets, debossed ‘ML’ and ‘62’ on either side of a deep scoreline and a scoreline on other side.

**Levofloxacin 500 mg film-coated tablets**
Peach colored, capsule shaped, biconvex, film coated tablets, debossed ‘ML’ and ‘63’ on either side of a deep scoreline and a scoreline on other side.

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, crospovidone (Type A), hypromellose (15cP) and magnesium stearate making up the tablet core; hypromellose (6cP)(E464), titanium dioxide (E171), macrogol 400, polysorbate 80 (E433), iron oxide red (E172) and (iron oxide yellow (E172)-only in 500 mg strength), making up the tablet coating. Appropriate justification for the inclusion of each of the excipients has been provided.

All the ingredients in the tablets comply with their relevant Ph.Eur monographs, with the exception of iron oxides (red and yellow) which comply with the National Formulary (NF). Satisfactory Certificates of Analysis for each of the excipients have been presented. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in the product, or used in the manufacturing process. Furthermore, no genetically modified organisms are used in the manufacture of the excipients.

**Pharmaceutical Development**
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop medicinal products bioequivalent and pharmaceutically equivalent to the reference products, Tavanic 250 mg and 500 mg film-coated tablets (PL 13042/0011-12, respectively, Sanofi Aventis, UK).

**Manufacture**
A description and flow-chart of the manufacturing method have been provided.
In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and were acceptable. Satisfactory analytical results from 2 consecutive production batches of each strength were provided.

**Dissolution and Impurity Profiles**
Dissolution and impurity profiles of the drug products were found to be similar to those for the reference products.

**Finished Product Specification**
Finished product specifications are provided for both release and shelf–life, and are satisfactory. These provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container Closure System**
The finished product is licensed for marketing in blister strips composed of polyvinylchloride (PVC) coated with polyvinylidene chloride (PVD) and aluminium which are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 5 or 10 tablets. Not all pack sized may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, with no specific storage conditions required for this medicinal product, which is satisfactory.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vita*, of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to understand the information that it contains.
MAA Form
The MAA form is satisfactory from a pharmaceutical perspective.

Conclusion
There are no objections to approval of Levofloxacin 250 mg and 500 mg Film-Coated Tablets from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

PHARMACOLOGY

GLP aspects
This application is based on well-established use and as such, no new non-clinical data are available. The GLP status of the published studies is not known.

Pharmacodynamic, pharmacokinetic and toxicological properties of levofloxacin hemihydrate are well known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

Environmental risk assessment
No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As these are generic products, the use of these products are not expected to increase the overall use of levofloxacin and so no additional increase in environmental risk has been identified.

Non-Clinical Overview
The non-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vita of the expert has been provided.

Summary of Product Characteristics (SmPC)
Section 4.6 and 5.3 are satisfactory from a non-clinical viewpoint.

There are no objections to approval of Levofloxacin 250 mg and 500 mg Film-Coated Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

In adults with infections of mild or moderate severity, Levofloxacin tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms (see section 5.1):

- 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.

**POSOLOGY AND METHOD OF ADMINISTRATION**

Levofloxacin 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.

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference products and is satisfactory.

**TOXICOLOGY**

The toxicology of levofloxacin is well-known. No new data have been submitted and none are required for these types of applications.

**Pharmacokinetics**

The applications are supported by a single bioequivalence study presented by the applicant, comparing the test product, Levofloxacin Tablets 500 mg with the reference product Tavanic (Levofloxacin Tablets 500 mg; Sanofi Aventis, UK) under fasting conditions.

**Biowaiver**

Satisfactory justification is provided for a bio-waiver for Levofloxacin 250 mg Film-Coated Tablets. As Levofloxacin 250 mg Film-Coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev1/Corr), the results and conclusions of the bioequivalence study on the 500 mg strength can be extrapolated to the 250mg strength tablets.

**Study**

This was an open label, single dose, balanced, randomised, two-treatment, two-period, crossover bioavailability study conducted in thirty healthy individuals under fasting conditions. Following an overnight fast of 10 hours, a single dose of the investigational products were administered orally, with water, to each subject in each period. A washout period of at least seven days separated the two dosing days.

**Pre-defined bioequivalence acceptance criteria**

Bioequivalence was to be concluded if the 90% Confidence Intervals for the ratios of the means of Ln-transformed pharmacokinetic parameters Cmax and AUCo-t for the test and reference formulations were within the bioequivalence limits of 80%-125%.
Analytical methods:
Blood samples were taken pre-dose and at specified time points up to 48 hours after administration of test or reference product. Samples were analysed for levofloxacin using a validated analytical method using a validated High Performance Liquid Chromatography (HPLC) methodology.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

Method of data analysis
Pharmacokinetic parameters (Tmax, Cmax, AUC0-t, AUC0-∞, lambda z, kel and t1/2) were calculated from the plasma levofloxacin concentrations by non-compartmental analysis. The 90% Confidence Intervals for the ratios of the means of Ln-transformed pharmacokinetic parameters Cmax and AUC0-t were also calculated.

Results
Bioequivalence results for Ln-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric mean (Test)</th>
<th>Geometric mean (Reference)</th>
<th>Ratio (T/R) (%)</th>
<th>90% Confidence Interval for Ln-transformed data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>6.705</td>
<td>5.822</td>
<td>96.00</td>
<td>92.50 - 103.82</td>
</tr>
<tr>
<td>AUC0-t (μg*hrs/mL)</td>
<td>42.896</td>
<td>42.980</td>
<td>96.80</td>
<td>98.58 - 101.04</td>
</tr>
<tr>
<td>AUC0-∞ (μg*hrs/mL)</td>
<td>46.571</td>
<td>47.014</td>
<td>96.91</td>
<td>98.58 - 101.26</td>
</tr>
</tbody>
</table>

Conclusion on bioequivalence study:
The results of the bioequivalence study show that Cmax and AUC of the test product fall within the acceptance criteria range of 80-125% in line with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Therefore the test product Levofloxacin 500 mg Film-Coated Tablets is bioequivalent with the reference product Tavanic (Levofloxacin Tablets 500 mg (Sanofi Aventis, UK). A biowaiver for Levofloxacin 250 mg Film-Coated Tablets is acceptable as discussed above.

Pharmacodynamics
No new pharmacodynamic data have been submitted and none are required for these applications.

Clinical efficacy
No new efficacy data have been submitted and none are required for these applications.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of levofloxacin is well-known.
**Post marketing experience**
The applicant’s Levofloxacin 250mg/500mg Film-coated Tablets have not been marketed in any country. Levofloxacin as an active ingredient has a well-established and an acceptable level of safety in the indications approved for the reference product, which was first authorised in EU in 1997.

**Expert Report**
A satisfactory clinical overall summary is provided, and has been prepared by an appropriately qualified physician. The *curriculum vita* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

**MAA form**
The MAA forms are medically satisfactory.

**Expert Report**
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vita* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs and PILs are acceptable from a clinical perspective and are consistent with those for the reference products. The labelling is clinically acceptable and is in-line with current requirements.

**MAA form**
The MAA form is satisfactory from a clinical perspective.

**Overall Conclusion**
The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Levofloxacin 500 mg Film-Coated Tablets) and reference (Tavanic 500 mg film-coated tablets- PL 13042/0012) products within the agreed acceptance limits under fasting conditions. A biowaiver for Levofloxacin 250 mg Film-Coated Tablets has been accepted. There are no objections to approval of Levofloxacin 250 mg and 500 mg Film-Coated Tablets from a clinical point of view.

Sufficient clinical information has been submitted to support these applications. When used as indicated, the products have a favourable benefit-to-risk ratio. Marketing Authorisations were therefore granted.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Levofloxacin 250 mg and 500 mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Levofloxacin 500 mg Film-Coated Tablets, and the reference product, Tavanic 500 mg Film-Coated Tablets (Sanofi-Aventis, UK) under fasting conditions. Given that linear kinetics apply between the 500 mg and 250 mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 250 mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference products. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears in the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Levofloxacin 250 mg and 500 mg Film-Coated Tablets and the reference products Tavanic 250 mg and 500 mg Film-Coated Tablets, (Sanofi-Aventis, UK-PL 13042/0011-12 respectively) are interchangeable. Extensive clinical experience with levofloxacin hemihydrate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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