# LEVOFLOXACIN 250MG FILM-COATED TABLETS
PL 17907/0218

# LEVOFLOXACIN 500MG FILM-COATED TABLETS
PL 17907/0219

## UKPAR

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The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal product Levofloxacin 250mg and 500mg Film-Coated Tablets on 11 November 2011. These products, to be available as prescription-only medicines (POM), can be used to treat infections of the:

- Sinuses
- Lungs in people with long-term breathing problems or pneumonia
- Urinary tract, including your bladder and kidneys
- Skin and underneath the skin, including muscles, which is sometimes called ‘soft tissue’
- Prostate gland, where you have a long-lasting infection

Levofloxacin belongs to a group of antibiotics called fluoroquinolones. Levofloxacin kills bacteria and can be used against various sorts of infections. Like all antibiotics, levofloxacin is only effective against some types of bacteria. So it is only suitable for treating some types of infection.

No new or unexpected safety concerns arose from these generic abridged applications and it was, therefore, judged that the benefits of taking Levofloxacin 250mg and 500mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Levofloxacin 250mg and 500mg Film-Coated Tablets (PL 17907/0218-9) could be approved.

The products are prescription-only medicines for the treatment of the following infections in adults when due to levofloxacin-susceptible microorganisms and of mild to moderate severity:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),
- Uncomplicated urinary tract infections
- Complicated urinary tract infections (including pyelonephritis)
- Chronic bacterial prostatitis
- Skin and soft tissue infections

These applications were submitted according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Tavanic 250mg and 500mg Tablets, which were originally granted licences in the UK on 6 June 1997 to Hoechst Marion Roussel, but are now licensed (via change of ownership procedures) to Sanofi-Aventis.

Levofloxacin is a fluoroquinolone antibiotic. 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 S-enantiomer of D-ofloxacin. Levofloxacin binds to DNA gyrase and DNA topoisomerase IV in bacteria, causing defective supercoiling of the DNA and also impairment of relaxation of supercoiling in chromosomes and plasmids.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

**PHARMACEUTICAL ASSESSMENT**

S.  **Active substance**

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

Structure:

![Structure of Levofloxacin Hemihydrate](image)

Molecular formula: \(C_{18}H_{20}FN_{3}O_{4}.\frac{1}{2}H_{2}O\)  
Molecular weight: 370.38  
Appearance: Light yellowish-white to yellow-white crystalline powder, soluble in sodium hydroxide solution

Levofloxacin hemihydrate has one chiral centre and exhibits polymorphism.

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.

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.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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 supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (Avicel PH101), microcrystalline cellulose (Avicel PH102), crospovidone (Kollidone CL), hypromellose, sodium stearyl fumarate, titanium dioxide (E 171), purified talc, ferric oxide red (E 172), ferric oxide yellow (E172) and polyethylene glycol – 400 (PEG 400).

With the exception of ferric oxide red and ferric oxide yellow, all excipients comply with their respective European Pharmacopoeia monograph. Ferric oxide red and ferric oxide yellow comply with their respective US National Formulary monographs and also comply with European guidelines concerning the use of colorants. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin and no genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable and stable tablets containing 250mg and 500mg levofloxacin hemihydrate that could be considered generic medicinal products to Tavanic 250mg and 500mg Tablets (Sanofi-Aventis).

A satisfactory account of the pharmaceutical development has been provided.

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

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System

Both strengths of tablets are packaged in clear polyvinylchloride/aluminium foil blister strips, which are enclosed in an outer carton. Each carton contains 1, 5 or 10 tablets. Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the UK regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of both strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the storage conditions “Do not store above 25°C. Store in the original packaging.”

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of marketing authorisations is recommended.
NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of levofloxacin hemihydrate are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Levofloxacin 500mg Tablets versus the reference product Tavanic 500mg Tablets in healthy adult volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The two treatment arms were separated by an 8-day washout period.

The pharmacokinetic results (non-transformed means and log-transformed ratios and 90% confidence intervals [CI]) are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Reference (R)</th>
<th>Test (T)</th>
<th>Ratio (T/R)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>5386</td>
<td>5283</td>
<td>102%</td>
<td>100-103</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>46553</td>
<td>47314</td>
<td>102%</td>
<td>100-103</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>52110</td>
<td>52931</td>
<td>98%</td>
<td>93-104</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.72</td>
<td>1.71</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AUCt  area under the plasma concentration-time curve from time zero to 72 hours
AUCt  area under the plasma concentration-time curve from time zero to infinity
Cmax maximum plasma concentration
Tmax time to maximum plasma concentration
90% geometric CI calculated from In-transformed data

The 90% confidence intervals for Cmax and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

As the 250mg and 500mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 500mg strength to the 250mg strength is justified.

Efficacy
No new data on the efficacy have been submitted and none are required for these types of applications.

Safety
No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL, Labels
The SmPC, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products.
Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Levofloxacin 250mg and 500mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type. A suitable justification has been provided for non-submission of an Environmental Risk Assessment.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s 500mg Tablets and its respective reference product. As the 250mg and 500mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the 250mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with levofloxacin hemihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**LEVOFLOXACIN 250MG FILM-COATED TABLETS**
**PL 17907/0218**

**LEVOFLOXACIN 500MG FILM-COATED TABLETS**
**PL 17907/0219**

**STEPS TAKEN FOR ASSESSMENT**

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on</td>
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<tr>
<td></td>
<td>20 December 2006</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the</td>
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<tr>
<td></td>
<td>MHRA considered the applications valid on 1 March 2007</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further</td>
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<tr>
<td></td>
<td>information relating to the quality dossier on 27 September 2007</td>
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<td></td>
<td>and 25 February 2009, and the clinical dossier on 22 March 2007,</td>
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<td></td>
<td>12 November 2008, 29 January 2009 and 1 March 2010</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further</td>
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<td>information relating to the quality dossier on 31 March 2008 and</td>
</tr>
<tr>
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<td>1 September 2009, and the clinical dossier on 23 September 2008,</td>
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<tr>
<td>5</td>
<td>The applications were determined on 11 November 2011</td>
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LEVOFLOXACIN 250MG FILM-COATED TABLETS
PL 17907/0218
LEVOFLOXACIN 500MG FILM-COATED TABLETS
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STEPS TAKEN AFTER ASSESSMENT

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Levofloxacin 250mg film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains Levofloxacin hemihydrate equivalent to Levofloxacin 250mg.

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets
(tablet)

Pink coloured, capsule shaped, biconvex film coated tablets with a break line on both sides.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),
- Uncomplicated urinary tract infections
- Complicated urinary tract infections (including pyelonephritis)
- Chronic bacterial prostatitis
- Skin and soft tissue infections

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

4.2 Posology and method of administration
Posology
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.

The following dose recommendations can be given for Levofloxacin:

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


<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage (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 pyelonephritis</td>
<td>250 mg once daily</td>
<td>7 – 10 days</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>500 mg once daily</td>
<td>28 days</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>250 mg once daily or 500 mg once or twice daily</td>
<td>7 – 14 days</td>
</tr>
</tbody>
</table>

**Special populations**

**Impaired renal function** (creatinine clearance ≤ 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>&gt;50-20 ml / min</td>
<td>first dose : 250 mg</td>
<td>then : 125 mg / 24 h</td>
<td>then : 250 mg / 24 h</td>
<td>then : 250 mg / 12 h</td>
</tr>
<tr>
<td>19 – 10 ml / min</td>
<td>first dose : 125 mg / 24 h</td>
<td>then : 125 mg / 48 h</td>
<td>then : 125 mg / 24 h</td>
<td>then : 125 mg / 12 h</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. (also see section 4.4 regarding QT interval prolongation).

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

**Duration of treatment**
The duration of therapy 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. 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 4.5: “Interactions”).

**4.3 Contraindications**
Levofloxacin 250mg film-coated tablets must not be used:
- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients listed in section 6.1
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
• in breast-feeding women

4.4 Special warnings and precautions for use
In the most severe cases of pneumococcal pneumonia Levofloxacin may not be the optimal therapy.

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

Methicillin resistant staphylococcus aureus (MRSA): Methicillin-resistant S. Aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (see section 5.1).

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

Tendinitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Levofloxacin tablets. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin tablet 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 ± 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 photosensitisation**
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

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

**Psychotic reactions**
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour—sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

**Cardiac disorders**

**QT interval prolongation**
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
(See section 4.2 elderly, section 4.5, section 4.8, section 4.9).

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

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

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

## 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 Levofloxacin 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 tablet 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 tablet 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 co-administered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

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

**Effect of Levofloxacin Tablets on other medicinal products**  

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

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

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

**Other forms of interactions**  

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

**4.6 Fertility, pregnancy and lactation**  

**Pregnancy**  
The product is contraindicated during pregnancy. Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets must not be used in pregnant women (see sections 4.3 and 5.3).
Breast-feeding
The product is contraindicated in breast-feeding women. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets must not be used in breast-feeding women (see sections 4.3 and 5.3)

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

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

The adverse reactions are described according to the MedDRA system organ class below. Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≥1/10000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Blood and lymphatic system disorders
Uncommon: Leucopenia, 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: Hypoglycaemia, 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: Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG (Electrocardiogram) QT prolonged (see section 4.4 QT interval prolongation and section 4.9)

**Vascular disorders**
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 (increase in serum activities of liver – derived enzymes) (e.g. ALT / AST, alkaline phosphatase, GGT)
Uncommon: Increase in serum concentration of bilirubin
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: Increase in serum concentration of creatinine
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 Levofoxacin 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: Anti-infectives for systemic use- Antibacterials for systemic use-Quinolone antibacterials-Fluroquinolone

ATC code: J01MA12

Levofoxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

**Mechanism of action**

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

**PK/PD relationship**

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (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 intermediate susceptible organisms and intermediate susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>≤ 2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Streptococcus A,B,C,G</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>H.influenzae</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M.catarrhalis</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
</tbody>
</table>
Non-species related breakpoints\(^3\) | ≤ 1 mg/L | > 2 mg/L
---|---|---
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.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive bacteria</strong></td>
</tr>
<tr>
<td>Staphylococcus aureus* methi-S</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
</tr>
<tr>
<td>Streptococci, group C and G</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pneumoniae *</td>
</tr>
<tr>
<td>Streptococcus pyogenes *</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative bacteria</strong></td>
</tr>
<tr>
<td>Burkholderia cepacia$</td>
</tr>
<tr>
<td>Eikenella corrodens</td>
</tr>
<tr>
<td>Haemophilus influenzae *</td>
</tr>
<tr>
<td>Haemophilus para-influenzae *</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td>Klebsiella pneumoniae *</td>
</tr>
<tr>
<td>Moraxella catarrhalis *</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>Providencia rettgeri</td>
</tr>
<tr>
<td><strong>Anaerobic bacteria</strong></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Chlamydomphila pneumoniae*</td>
</tr>
<tr>
<td>Chlamydomphila psittaci</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>Legionella pneumophila*</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae*</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
</tr>
</tbody>
</table>
Species for which acquired resistance may be a problem

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

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

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

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

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

5.2 Pharmacokinetic properties

Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1hr 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/ml and 10.8 μg/ml respectively. These were reached approximately one hour after administration.

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

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

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

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

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

Elimination
Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t1/2 : 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 impairment
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below :

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

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

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

5.3 Preclinical safety data
Acute toxicity
The median lethal dose (LD50) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500 – 2000 mg / kg.

Administration of 500 mg / kg p.o. to monkeys induced little effect apart from vomiting.

Repeated dose toxicity
Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg / kg / day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100mg/kg/day and 10,25,62.5 mg/kg/day for 1 to 6 months in the monkey.
Signs of reaction to treatment were minor in the rat with slight effect principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The No Observed Adverse effect Level (NOELs) in these studies were conducted to be 200 and 20 mg/kg/day after 1 and 6 months respectively.

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

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

Reproductive toxicity
Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day or intravenous doses up to 100 mg/kg/day.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day.

Levofloxacin had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Levofloxacin 250mg film-coated tablets contain the following excipients:
- Microcrystalline cellulose (Avicel PH101)
- Microcrystalline cellulose (Avicel PH102)
- Crospovidone (Kollidone CL)
- Hypromellose
- Sodium stearyl fumarate
- Titanium dioxide (E 171)
- Purified talc
- Ferric oxide red (E 172)
- Ferric oxide yellow (E172)
- Polyethylene glycol – 400 (PEG 400)
6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Clear PVC / Aluminium foil, pack sizes of 1’s, 5’s, 10’s.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/11/2011

10 DATE OF REVISION OF THE TEXT
11/11/2011
1 NAME OF THE MEDICINAL PRODUCT
Levofloxacin 500mg film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains Levofloxacin hemihydrate equivalent to Levofloxacin 500mg.
For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets
(pink coloured, capsule shaped, biconvex film coated tablets with a break line on both sides.

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:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),
- Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection),
- Uncomplicated urinary tract infections
- Complicated urinary tract infections (including pyelonephritis)
- Chronic bacterial prostatitis
- Skin and soft tissue infections

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

4.2 Posology and method of administration
Posology
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.

The following dose recommendations can be given for Levofloxacin:

<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>Complicated urinary tract infections including pyelonephritis</td>
<td>250 mg once daily</td>
<td>7 - 10 days</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td>500 mg once daily</td>
<td>28 days</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>250 mg once daily or 500</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg / 24 h</td>
</tr>
<tr>
<td>50-20 ml / min</td>
<td>then : 125 mg / 24 h</td>
</tr>
<tr>
<td>19 – 10 ml / min</td>
<td>then : 125 mg / 48 h</td>
</tr>
<tr>
<td>&lt; 10 ml / min (including haemodialysis and CAPD)</td>
<td>then : 125 mg / 48 h</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. (also see section 4.4 regarding QT interval prolongation).

In children

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

Duration of treatment

The duration of therapy 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. 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 4.5: “Interactions”).

4.3 Contraindications

Levofloxacin 500mg film-coated tablets must not be used:
- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients listed in section 6.1
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
- in breast-feeding women

4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia Levofloxacin may not be the optimal therapy.

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

Methicillin resistant staphylococcus aureus (MRSA):
Methicillin-resistant S. Aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (see section 5.1).

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

**Tendinitis and tendon rupture**
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendonitis 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 tablet 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 ± 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 photosensitisation**
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

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

**Psychotic reactions**
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

**Cardiac disorders**
**QT interval prolongation**
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
(See section 4.2 elderly, section 4.5, section 4.8, section 4.9).

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

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

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

### 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 Levofloxacin 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 tablet 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 tablet 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 co-administered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

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

**Effect of Levofloxacin Tablets on other medicinal products**

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

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

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

**Other forms of interactions**

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

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**
The product is contraindicated during pregnancy. Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets must not be used in pregnant women (see sections 4.3 and 5.3)

**Breast-feeding**
The product is contraindicated in breast-feeding women. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets must not be used in breast-feeding women (see sections 4.3 and 5.3)

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

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

The adverse reactions are described according to the MedDRA system organ class below. Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≥1/100000), 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: Leucopenia, 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: Hypoglycaemia, 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: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG (Electrocardiogram) QT prolonged (see section 4.4 QT interval prolongation and section 4.9)

Vascular disorders
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 (increase in serum activities of liver—derived enzymes) (e.g. ALT / AST, alkaline phosphatase, GGT)
Uncommon: increase in serum concentration of bilirubin
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

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: increase in serum concentration of creatinine
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: Anti-infectives for systemic use - Antibacterials for systemic use - Quinolone antibacterials - Fluoroquinolone

ATC code: J01MA12

Levofoxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin.

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

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (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><em>Pseudomonas</em> <em>spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter</em> <em>spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus</em> <em>spp.</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S.pneumoniae</em></td>
<td>≤ 2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Streptococcus</em> <em>A,B,C,G</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>H.influenzae</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M.catarrhalis</em></td>
<td>≤ 1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
</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* methi-S
- *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
- *Chlamydophila pneumoniae*
- *Chlamydophila psittaci*
- *Chlamydia trachomatis*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- *Mycoplasma hominis*
- *Ureaplasma urealyticum*
### Species for which acquired resistance may be a problem

<table>
<thead>
<tr>
<th>Aerobic Gram-positive bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis*</td>
</tr>
<tr>
<td>Staphylococcus aureus methicillin-resistant</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus methicillin resistant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aerobic Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii *</td>
</tr>
<tr>
<td>Citrobacter freundii *</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
</tr>
<tr>
<td>Enterobacter agglomerans</td>
</tr>
<tr>
<td>Enterobacter cloacae *</td>
</tr>
<tr>
<td>Escherichia coli *</td>
</tr>
<tr>
<td>Morganella morganii *</td>
</tr>
<tr>
<td>Proteus mirabilis*</td>
</tr>
<tr>
<td>Providencia stuartii</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa*</td>
</tr>
<tr>
<td>Serratia marcescens*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaerobic bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides fragilis</td>
</tr>
<tr>
<td>Bacteroides ovatus$</td>
</tr>
<tr>
<td>Bacteroides thetaiotamicton$</td>
</tr>
<tr>
<td>Bacteroides vulgatus$</td>
</tr>
<tr>
<td>Clostridium difficile$</td>
</tr>
</tbody>
</table>

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

$ natural intermediate susceptibility

### 5.2 Pharmacokinetic properties

**Absorption**

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 hr. 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/ml and 10.8 μg/ml respectively. These were reached approximately one hour after administration.

**Penetration into Lung Tissue**

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

**Penetration into Blister Fluid**

Maximum levofloxacin concentrations of about 4.0 and 6.7 μg/ml in the blister fluid were reached 2 – 4 hours after administration following 3 days dosing at 500 mg once or twice daily, respectively.
**Penetration into Cerebro-Spinal Fluid**
Levofloxacin has poor penetration into cerebro-spinal fluid.

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

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

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

**Elimination**
Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t1/2 : 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 impairment**
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below :

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

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

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

5.3 **Preclinical safety data**

**Acute toxicity**
The median lethal dose (LD50) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500 – 2000 mg / kg.

Administration of 500 mg / kg p.o. to monkeys induced little effect apart from vomiting.

**Repeated dose toxicity**
Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg / kg / day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100mg/kg/day and 10,25,62.5 mg/kg/day for 1 to 6 months in the monkey.
Signs of reaction to treatment were minor in the rat with slight effect principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The No Observed Adverse effect Level (NOELs) in these studies were conducted to be 200 and 20 mg/kg/day after 1 and 6 months respectively.

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

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

Reproductive toxicity
Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day or intravenous doses up to 100 mg/kg/day.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day.

Levofloxacin had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

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

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

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Levofloxacin 500mg film-coated tablets contain the following excipients:
- Microcrystalline cellulose (Avicel PH101)
- Microcrystalline cellulose (Avicel PH102)
- Crospovidone (Kollidone CL)
- Hypromellose
- Sodium stearyl fumarate
- Titanium dioxide (E 171)
- Purified talc
- Ferric oxide red (E 172)
- Ferric oxide yellow (E172)
- Polyethylene glycol – 400 (PEG 400)
6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Clear PVC / Aluminium foil, pack sizes of 1’s, 5’s, 10’s.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0219

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/11/2011

10 DATE OF REVISION OF THE TEXT
11/11/2011
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR USER

LEVOFLOXACIN 250mg & 500mg FILM-COATED TABLETS
Active Substance: Levofloxacin hemihydrate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any side effects get 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 film-coated tablets are and what they are used for
2. Before you take Levofloxacin film-coated tablets
3. How to take Levofloxacin film-coated tablets
4. Possible side-effects
5. How to store Levofloxacin film-coated tablets
6. Further information

1. What Levofloxacin Tablets are and what are they used for

Levofloxacin is an antibiotic. It belongs to a group of antibiotics that are called fluoroquinolones. Levofloxacin kills bacteria and it can be used against various sorts of infections. Like all antibiotics, Levofloxacin is only effective against some types of bacteria. So, it is only suitable for treating some types of infection.

Levofloxacin can be used to treat infections of the:
- Sinuses
- Lungs, in people with long-term breathing problems or pneumonia
- Urinary tract, including your bladder or kidneys
- Skin and underneath the skin, including muscles. This is sometimes called ‘soft tissue’
- Prostate gland, where you have a long lasting infection

taking any of the following medicines. This is because it can increase the chance of you getting side effects, when taken with Levofloxacin tablets:
- Corticosteroids, sometimes called steroids—used for inflammation. You may be more likely to have inflammation and/or breakage of your tendons.
- Warfarin—used to thin the blood. You may be more likely to have a bleed. Your doctor may need to take regular blood tests to check how well your blood can clot.
- Theophylline—used for breathing problems. You are more likely to have a fit (seizure) if taken with levofloxacin tablets
- Non-steroidal anti-inflammatory drugs (NSAIDS)—used for pain and inflammation such as aspirin, ibuprofen, fenbufen, ketoprofen and indometacin. You are more likely to have a fit (seizure) if taken with levofloxacin tablets
- Ciclosporin—used after organ transplants. You may be more likely to get the side effects of Ciclosporin
- Probencid—used for gout, and cimetidine—used for ulcers and heartburn. Special care should be taken when taking either of these medicines with Levofloxacin. If you have kidney problems, your doctor may want to give you a lower dose.
- You must tell your doctor if you are taking other medicines that can alter your heart rhythm; medicines that belong to the group of anti-arrhythmic (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants, some antimicrobials (that belong to the group of macrodides).

Do not take Levofloxacin tablets at the same time as the following medicines. This is because it can affect the way Levofloxacin tablets work:
- Iron tablets (for anaemia), magnesium or aluminium-containing antacids (for acid or heartburn) or sulcrafate (for stomach ulcers). See Section 3 “If you are already taking iron tablets, antacids or sulcrafate” below.

Urine tests for opiates
Urine tests may show ‘false-positive’ results for strong painkillers called ‘opiates’ in people taking Levofloxacin tablets. If your doctor is due to take a urine test, tell them you are taking Levofloxacin tablets.

Pregnancy and breast-feeding
Do not take this medicine if:
2. Before you take Levofloxacin tablets

Do not take the Levofloxacin tablets if you:
- are allergic to Levofloxacin, or any other quinolone antibiotic such as moxifloxacin, ciprofloxacin or ofloxacin or to any of the other ingredients of the levofloxacin tablets (listed in Section 6, Further Information)
- Signs of an allergic reaction include: a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue
- have ever had epilepsy
- have ever had tendon problems (e.g. tendonitis) related to treatment with a 'quinolone antibiotic'. A tendon is the cord that joins your muscle to your skeleton
- are pregnant, might become pregnant or think you may be pregnant
- are breast-feeding
- are a child or growing teenager

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 film-coated tablets.

Take special care and check with your doctor or pharmacist before taking Levofloxacin tablets if:
- You are 65 years of age or older
- You are using corticosteroids, sometimes called steroids (see "Taking other medicines" below)
- You have ever had a fit (seizure)
- You have had damage to your brain due to stroke or other brain injury
- You have kidney problems
- You have something known as 'glucose-6 phosphate dehydrogenase deficiency'. You are more likely to have serious problems with your blood when taking this medicine
- You have ever had mental health problems
- You are diabetic
- You have ever had liver problems

Heart problems

Caution should be taken when using this kind of medicine. If you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called ‘bradycardia’), have a weak heart (heart failure), have a history of heart attack (myocardial infarction), you are female or elderly or you are taking other medicines that result in abnormal ECG changes (see section Taking other medicines).

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Levofloxacin tablets.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you take without a prescription including herbal medicines. This is because levofloxacin tablets can affect the way some other medicines work. Also some medicines can affect the way levofloxacin tablets work. In particular, tell your doctor if you are
- 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 blisters 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 sulcralfate
- Do not take these medicines at the same time as levofloxacin. 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
- Two tablets of Levofloxacin 250 mg, once each day
- Or, one tablet of Levofloxacin 500 mg, once each day

Lungs, in people with long-term breathing problems
- One or two tablets of Levofloxacin 250 mg, once each day
- Or, 1/2 tablet or one tablet of Levofloxacin 500 mg, once each day

Pneumonia
- Two tablets of Levofloxacin 250 mg, once or twice each day
- Or, one tablet of Levofloxacin 500 mg, once or twice each day
Urinary tract, including your kidneys or bladder
- One tablet of Levofloxacin 250 mg, each day
- Or, ½ tablet of Levofloxacin 500 mg, each day

Prostate gland
- Two tablets of Levofloxacin 250 mg, once each day
- Or, one tablet of Levofloxacin 500 mg, once each day

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

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

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

If you take more Levofloxacin film-coated 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, altered consciousness and heart problems leading to uneven heart beats as well as feeling sick (nausea).

If you forget to take Levofloxacin film-coated 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 to make up for the missed dose.

If you stop taking Levofloxacin film-coated tablets
Do not stop taking Levofloxacin film-coated 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 can cause side effects, although not everybody gets them. These effects are normally mild or moderate and often disappear after a short time.

- Feeling stressed (anxiety), depressed, mental problems, feeling restless (agitation) or feeling confused
- Unusual fast beating of your heart or low blood pressure
- 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 (dyspnoea)
- Severe itching or hives (called urticaria)

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 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

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.
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, swallowing 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. 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’

Not known (frequency cannot be estimated from the available data)

- **Heart Problems**—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)
  - Severe skin rashes which may include blistering or peeling of the skin around your lips, eyes, mouth, nose and genitalia
  - Stop taking Levofloxacin tablets and see a doctor straight away (continued):
    - 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

**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)
- Tingly feeling in your hands and feet (paraesthesia) or trembling

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5. How to store Levofloxacin Film-Coated Tablets

- Keep out of the reach and sight of children
- Do not store above 25°C
- Store in the original package or container in order to protect from light and moisture
- Do not use these tablets after expiry date (exp) printed on the pack. The expiry date refers to the last day of that month
- 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 Levofloxacin film-coated tablets contain

Each film-coated tablet contains 250mg or 500mg of the active ingredient, Levofloxacin hemihydrate

The other ingredients are: Microcrystalline cellulose (Avicel PH101), Microcrystalline cellulose (Avicel PH102), Crospovidone, hypromellose, Sodium stearyl fumarate, Titanium dioxide (E 171), Purified talc, Ferric oxide red (E172), Ferric oxide yellow (E172), Polyethylene glycol – 400 (PEG 400).

What Levofloxacin film-coated tablets look like and contents of the pack

The 250 mg tablets are pink coloured, capsule shaped, biconvex film-coated tablets with a breakline on both the sides. The 500 mg tablets are pink coloured, capsule shaped, biconvex film-coated tablets with a breakline on both the sides.

The tablets are packaged in clear blister packs of 1, 5 or 10 tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

Name and Address:
Bristol Laboratories Limited,
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Hertfordshire, HP4 1EG,
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Tel: 0044 (0) 1442 200922
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Levofloxacin 250mg Film-Coated Tablets, PL 17907/0218
Levofloxacin 500mg Film-Coated Tablets, PL 17907/0219

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