LEVOFLOXACIN 250MG FILM-COATED TABLETS
PL 19156/0045

LEVOFLOXACIN 500G FILM-COATED TABLETS
PL 19156/0046

UKPAR

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LEVOFLOXACIN 250MG FILM-COATED TABLETS  
PL 19156/0045  

LEVOFLOXACIN 500G FILM-COATED TABLETS  
PL 19156/0046

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Jubilant Pharmaceuticals nv Marketing Authorisations (licences) for the medicinal products Levofloxacin 250mg Film Coated Tablets (PL 19156/0045) and Levofloxacin 500mg Film Coated Tablets (PL 19156/0046) on 25th November 2009. These prescription-only medicines (POM) are used to treat bacterial infections of the skin and soft tissue, respiratory tract infections and other generalised infections.

The active ingredient, levofloxacin, belongs to a group of medicines called antibiotics. Levofloxacin is a “quinolone” antibiotic. It works by killing the bacteria that cause infections in the body. Levofloxacin film coated tablets can be used to treat infections of the sinuses; the lungs in people with long term breathing problems; the urinary tract, including the kidneys or bladder; long lasting infections of the prostrate gland and infections of the skin and muscles (soft tissue).

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Levofloxacin 250mg Film Coated Tablets and Levofloxacin 500mg Film Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
LEVOFLOXACIN 250MG FILM-COATED TABLETS
PL 19156/0045

LEVOFLOXACIN 500G FILM-COATED TABLETS
PL 19156/0046

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Levofloxacin 250mg Film Coated Tablets (PL 19156/0045) and Levofloxacin 500mg Film Coated Tablets (PL 19156/0046) to Jubilant Pharmaceuticals nv on 25th November 2009. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The products are claimed to be generic medicinal products of the reference products, Tavanic 250mg, film-coated tablets (PL 13402/0011) and Tavanic 500mg, film-coated tablets (PL 13402/0012), licensed to Hoechst Marion Roussel Ltd in the UK. The reference products have been authorised in the EEA for over 10 years. The licenses were originally granted on 6th June 1997. Bioequivalence to the reference product has been demonstrated using the German reference product- Tavanic, 500mg film-coated tablets.

The products contain the active ingredient levofloxacin, which is a synthetic antibacterial agent of the fluoroquinolone class. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV which is an enzyme to separate replicate DNA, thereby inhibiting cell division.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Levofloxacin
INN/ BAN/ USAN: 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.

CAS No: 138199-71-0

Structure

![Molecular Structure of Levofloxacin Hemihydrate]

Molecular formula: C_{18}H_{20}FN_{3}O_{4}.\frac{1}{2}H_{2}O
Molecular weight: 370.38

General Properties

Description: Almost white to light yellow crystalline powder

Polymorphism: According to literature Levofloxacin exhibits polymorphism and different hydrates such as anhydrous, hemi hydrate and monohydrate forms.

Chirality: Levofloxacin hemihydrate has one chiral centre.

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

Levofloxacin complies with in-house specifications.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance levofloxacin.
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

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

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

An appropriate specification is provided for the active substance levofloxacin, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

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

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug and supporting an appropriate re-test period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely crospovidone, hypromellose, microcrystalline cellulose, talc and magnesium stearate. All ingredients within the core of the tablet comply with relevant Ph. Eur monographs.

The film-coating consists of: hypromellose, titanium dioxide, talc, macrogol, iron oxide yellow and iron oxide red. All the ingredients comply with relevant Ph. Eur monographs or in-house specifications.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

None of the excipients used contains material of animal or human origin.

There were no novel excipients used and no overages.

**Pharmaceutical Development**

The objective of the pharmaceutical development of this product was to develop bioequivalent and stable formulations comparable to the innovator’s products Tavanic 250mg and 500mg film coated tablets.

The applicant has provided suitable product development sections. Justifications for the use of each excipient have been provided and are valid.

*Biowaiver for the 250mg strength tablets.*
The bioequivalence study was performed comparing the 500mg product to the innovator (German product).

The applicant has only included the 500 mg strength in the bioequivalence study. Pharmaceutically, the biowaiver acceptance criteria have been fulfilled:

- The 250mg strength is manufactured by the same manufacturer using the same process.
- The qualitative composition of 250mg strength is the same as for the bioequivalence batch.
- The ratio between amounts of active substance and excipients for the 250mg strength is the same as for the bioequivalence batch.
- The dissolution profile for the 250mg strength is similar to that of the bioequivalence batch

**Bioequivalence Study**

The study was an open labelled, balanced, randomised, two treatment, two-period, two sequence, single dose, two-way cross-over of the 500mg tablets in healthy volunteers.

The results showed the formulations to be bioequivalent and in line with the EU acceptance interval of 80%-125%. Further discussion is provided in the medical assessment. The data is provided in table 3

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Test Product-B</th>
<th>Reference Product-A</th>
<th>Ratio (B/A) %</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mcg / mL)</td>
<td>6.665</td>
<td>6.394</td>
<td>104.2</td>
<td>99.58 – 109.12%</td>
</tr>
<tr>
<td>AUC0-t (mcg.h / mL)</td>
<td>56.634</td>
<td>55.236</td>
<td>102.5</td>
<td>101.07 – 104.01%</td>
</tr>
<tr>
<td>AUC∞ (mcg.h / mL)</td>
<td>58.545</td>
<td>57.389</td>
<td>102.0</td>
<td>100.55 – 103.50%</td>
</tr>
</tbody>
</table>

Table 3: Pharmacokinetic data from the bioequivalence study between the test and reference product

**Dissolution and impurity profiles**

Dissolution and impurity profiles for the drug product were found to be similar to those for the reference product.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches of 250 mg film-coated tablets and batches of the 500 mg film-coated tablets have been provided. A commitment that the first three full scale batches produced of each strength will be validated is provided.
Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch analysis data for two pilot scale batches of both strength of tablets has been provided and demonstrates compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
All strengths of tablet are packaged in polyvinylchloride/aluminium blister strips in pack sizes of 7, 10 or 50 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Stability studies were performed on two pilot scale batches of the finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 18 months, with no specific storage conditions, which is satisfactory. A commitment is provided to place the first three full scale batches of each strength on stability trials. The applicant also commits to complete the ongoing trials.

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

MAA form
The MAA form is pharmaceutically satisfactory.

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

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.
INTRODUCTION

Clinical Background
The pharmacodynamic and pharmacokinetic properties of levofloxacin are well known. As levofloxacin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is thus appropriate.

The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical dossier.

Indications
Levofloxacin is effective in the treatment of respiratory tract infections (acute sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, and nosocomial pneumonia), skin infections, urinary tract infections and prostatitis, mycobacterial infections, urogenital infections (including chlamydial infections, non-gonococcal urethritis), pelvic inflammatory disease, plague, travellers’ diarrhoea, and ophthalmic infections.

Dose and Dose Regimen
The usual oral dose is 250 or 500 mg once or twice daily. Doses should be reduced in patients with renal impairment.

GCP Aspects
The applicant provides assurance that the clinical study was performed according to the principles of Good Clinical Practice.

CLINICAL PHARMACOLOGY
Pharmacokinetics
Levofloxacin is rapidly and almost completely absorbed following oral use with peak plasma concentrations achieved within 1 hour of a dose. The absolute oral bioavailability of levofloxacin is approximately 99%. Levofloxacin pharmacokinetics are linear after single and multiple oral dosing regimens. The mean ± standard deviation peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 mg/ml after the 500 mg doses. Oral administration of 500 mg levofloxacin with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, levofloxacin tablets can be administered without regard to food. It is recommended that levofloxacin oral solution be taken 1 hour before, or 2 hours after eating.
Levofloxacin is distributed into body tissues including the bronchial mucosa and lungs, but penetration into cerebrospinal fluid is poor (concentrations approximately 16% of simultaneous plasma values). The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L.
Levofloxacin is approximately 30 to 40% bound to plasma proteins. Binding to serum proteins is independent of the drug concentration. Accumulation is negligible at 500 mg once daily multiple dosing. There is modest but predictable accumulation of levofloxacin at 500 mg twice daily. Steady-state is achieved within 3 days. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity. The plasma elimination half-life ranges from 6-8 hours in individuals with normal renal function. This may be prolonged in patients with renal impairment.

The mean apparent total body clearance and renal clearance range from approximately 144 to 226 ml/min and 96 to 142 ml/min, respectively. Approximately 80% of drug is eliminated unchanged in urine through glomerular filtration and tubular secretion. It is not removed by haemodialysis or peritoneal dialysis.

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

Bioequivalence
Test Product

Test Product-B : Levofloxacin Tablets 500 mg
Each film coated tablets containing 512.46 mg of Levofloxacin hemihydrate equivalent to 500 mg of Levofloxacin.

Reference Product
Reference Product-A : Tavanic ® (Levofloxacin 500 mg Tablets)
Each film coated tablet containing 512.46 mg of levofloxacin hemihydrate equivalent to 500 mg Levofloxacin.

Assessor’s comment
The biowaver is acceptable as levofloxacin fulfils the pharmaceutical criteria (see Quality report) and has linear kinetics over the clinically relevant dose range.

Study design
A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioequivalence study in healthy, adult, male subjects under fasting conditions.

Population(s) studied and clinical part of the study
36 healthy volunteers with an age range from 21- 43 years were enrolled in the study. All volunteers completed both study periods. All subjects who completed the study were included in the bioequivalence and the safety analysis.

The study drug was administered after an overnight fast of 10h. Blood samples for analyses were collected before dosing and up to 36 hours post-dose. There was a washout period of 7 days between study drug administrations.
**Assessor's comment:**

Single dose fasting studies are appropriate as there is no significant food effect on the bioavailability of levofloxacin. The chosen strength of the test and reference formulation was appropriate. The design of the study and the population chosen are acceptable. Inclusion and exclusion criteria were presented and acceptable. The randomization scheme was provided and appears acceptable.

Considering the elimination half-life of levofloxacin, the washout period is expected to be long enough to avoid any carry-over effects. The sampling period and sampling scheme seem adequate to estimate PK parameters.

**Pharmacokinetic Variables and Statistical methods**

The relevant pharmacokinetic parameters of this trial were Cmax, AUCT and AUC∞, additional parameters measured were AUC% extrapol, Kel, Tmax and T½el. Actual time points were considered for PK and statistical analysis. Bioequivalence of Test Product-B vs. Reference Product-A was concluded, if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Levofloxacin.

**Analytical methods**

The pharmacokinetics of each formulation was evaluated by the estimation of levofloxacin in plasma. A High Performance Liquid Chromatography with MS/MS detection in human plasma was used.

**Assessor's comment:**

The pharmacokinetic variables follow the current European standard and are appropriate for this study. The statistics is adequately described. The protocol specified 80-125% as criteria for bioequivalence. The data evaluation follows regulatory standards. Actual sampling times were used to calculate PK parameters, which is acceptable.

The analytical method used for quantification of levofloxacin in the bioequivalence study allows accurate and reproducible quantification. The analytical validation is of an acceptable standard. None of the pre-dose samples contained detectable levels of levofloxacin, the length of the washout period was adequate.

**Results**

**Safety**

Two post dose adverse events were reported and both were graded as mild in severity. The relationship of one event was judged as possible and one as unrelated. Upon conclusion of the clinical portion of the study, the results from all subjects who completed post-study procedures, confirmed the absence of significant changes in the subjects' state of health. There were no serious or significant adverse events reported during the course of the trial.


Efficacy

Table-A: Descriptive Statistics of Formulation Means for Levofloxacin (n=36)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)*</td>
<td>1.375</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (mcg / mL)</td>
<td>6.520 ± 1.3081</td>
</tr>
<tr>
<td>( \text{AUC}_{0,4} ) (mcg.h / mL)</td>
<td>55.578 ± 6.2249</td>
</tr>
<tr>
<td>( \text{AUC}_{0,\infty} ) (mcg.h / mL)</td>
<td>57.771 ± 6.7565</td>
</tr>
<tr>
<td>( \lambda_{\text{d}} ) (1 / h)</td>
<td>0.095 ± 0.0085</td>
</tr>
<tr>
<td>( t_{\text{lag}} ) (h)</td>
<td>7.337 ± 0.6968</td>
</tr>
<tr>
<td>AUC_% Extrap_Obs (%)</td>
<td>3.734 ± 1.9144</td>
</tr>
</tbody>
</table>

*\( T_{\text{max}} \) is represented in median value.

Table-B: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Levofloxacin (n=36)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (mcg / mL)</td>
<td>6.665</td>
<td>6.394</td>
</tr>
<tr>
<td>( \text{AUC}_{0,4} ) (mcg.h / mL)</td>
<td>56.634</td>
<td>55.236</td>
</tr>
<tr>
<td>( \text{AUC}_{0,\infty} ) (mcg.h / mL)</td>
<td>58.545</td>
<td>57.389</td>
</tr>
</tbody>
</table>

Assessor's Conclusion on Bioequivalence

The Bioequivalence study submitted by the applicant was performed according to the respective Note for Guidance and GCP requirements. A standard bioequivalence study with two-period, two-sequence crossover design was conducted. The study design was adequate to address the bioequivalence of an immediate release oral formulation with pharmacokinetic parameters of levofloxacin. Single dose fasting studies are appropriate as there is no significant food effect on the bioavailability of levofloxacin. The chosen strength of the test and reference formulation was appropriate.
The Test Product-B (Levofloxacin 500 mg Tablets) when compared with the Reference Product-A [Tavanic® (Levofloxacin 500 mg Tablets) meets the bioequivalence criteria with respect to the rate and extent of absorption of Levofloxacin. The investigational drugs were well tolerated by healthy subjects, as a single dose administration and no relevant differences in the safety profiles of the test and reference formulation were observed.

**Post marketing experience**
No post-marketing data is available. The medicinal product has not been marketed in any country. Levofloxacin has a recognised efficacy and an acceptable level of safety in the approved indication for the reference product, which was first authorised in the UK in 1997.

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

**PSUR**
The applicant proposes the harmonisation of the Periodic Safety Update Report (PSUR) birth date to the date of the first Marketing Authorisation grant in the EEA. The EU HBD (harmonised birth date) is 01/10/1993. The periodicity for PSUR preparation will therefore be calculated from this date with the next data lock being 10/2012.

**Risk Management System**
Levofloxacin tablets are generic products. No specific risks are related to levofloxacin as an active ingredient. A risk management plan is therefore not required.

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**Assessor’s comment**
The active ingredient levofloxacin has a well established safety profile. A 3 year PSUR cycle is therefore acceptable.

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**PRODUCT LITERATURE**

**SPC**
This is medically acceptable.

**Patient Information Leaflet**
This is medically acceptable.

**Labelling**
This is medically acceptable.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

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

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

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with levofloxacin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>1</strong></td>
<td>The MHRA received the marketing authorisation application on 11th September 2008.</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 30th September 2008.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 13th August, 1st September, 15th September 2009 for the clinical section on 15th July 2009, 13th August 2009 and 22nd October 2009.</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>The application was determined on 25th November 2009.</td>
</tr>
</tbody>
</table>
LEVOFLOXACIN 250MG FILM-COATED TABLETS  
PL 19156/0045

LEVOFLOXACIN 500G FILM-COATED TABLETS  
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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</table>
LEVOFLOXACIN 250MG FILM-COATED TABLETS
PL 19156/0045

SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet of Levofloxacin 250 mg contains 250 mg of levofloxacin as active substance corresponding to 256.23 mg of levofloxacin hemihydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Levofloxacin 250 mg film-coated tablets:
Light peach coloured film-coated tablets scored on both sides and debossed with “J” and “250” on either side of the scoreline on one side of the tablet.
The tablet can be divided in two equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults with infection of mild or moderate severity levofloxacin 250 mg is indicated for the treatment of the following infections when due to levofloxacin-susceptible micro-organisms:
- Acute sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Community-acquired pneumonia
- 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
Levofloxacin 250 mg is administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

Duration of treatment
The duration of treatment varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin 250 mg 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 250 mg should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or
between meals. Levofloxacin 250 mg should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

**Posology**

The following dose recommendations can be given for Levofloxacin 250 mg:

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Daily dose regimen (according to severity)</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute sinusitis</td>
<td>500 mg once daily</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Acute exacerbations of chronic bronchitis</td>
<td>250 to 500 mg once daily</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>500 mg once or twice daily</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Uncomplicated urinary tract infections</td>
<td>250 mg once daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Complicated urinary tract infections including 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>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg/24 h</td>
<td>500 mg/24 h</td>
</tr>
<tr>
<td>first dose: 250 mg</td>
<td>first dose: 500 mg</td>
</tr>
<tr>
<td>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 (see section 4.4 QT interval prolongation).

**In children**

Levofloxacin 250 mg is contraindicated in children and growing adolescents (see section 4.3).
4.3 Contraindications
Levofloxacin 250 mg must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
- in breast-feeding women.

4.4 Special warnings and precautions for use
In the most severe cases of pneumococcal pneumonia Levofloxacin 250 mg may not be the optimal therapy.
Nosocomial infections due to *P. aeruginosa* may require combination therapy.

*Tendinitis and tendon rupture*
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Levofloxacin 250 mg. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin 250 mg 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 250 mg, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Levofloxacin 250 mg must be stopped immediately and patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

*Patients predisposed to seizures*
Levofloxacin 250 mg is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system 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 250 mg 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 in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly (see section 4.5).

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

QT interval prolongation
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome,
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides),
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia),
- elderly,
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Effect of other medicinal products on Levofloxacin 250 mg

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 250 mg. 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 250 mg administration (see section 4.2). No interaction was found with calcium carbonate.

Sucralfate
The bioavailability of Levofloxacin 250 mg is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levofloxacin 250 mg, it is best to administer sucralfate 2 hours after the Levofloxacin 250 mg administration (see section 4.2).

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

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

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

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

**Other relevant information**

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

**Effect of Levofloxacin 250 mg 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 250 mg may therefore be administered regardless of food intake.

**4.6 Pregnancy and lactation**

**Pregnancy**

Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin 250 mg must not be used in pregnant women.

**Lactation**

In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin 250 mg must not be used in breast-feeding women.
4.7 Effects on ability to drive and use machines
Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient’s ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects
The information given below is based on data from clinical studies in more than 5,000 patients and on extensive post-marketing experience.
The adverse reactions are described according to the MedDRA system organ class below.
Frequencies are defined using the following convention:
Very common (≥1/10),
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, ≤1/100),
Rare (≥1/10,000, ≤1/1,000)
Very rare (≤1/10,000),
Not known (cannot be estimated from the available data).

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

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

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not Known</td>
</tr>
</tbody>
</table>

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

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

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

**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

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

**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

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

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

**Vascular disorders**
- Rare: Hypotension

**General disorders and administration site conditions**
- Uncommon: Asthenia
- Very rare: Pyrexia
- Not Known: Pain (including pain in back, chest, and extremities)
### Immune system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Anaphylactic shock (see section 4.4). Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.</td>
</tr>
<tr>
<td>Not known</td>
<td>Hypersensitivity (see section 4.4)</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

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

### Psychiatric disorders

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

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

### 4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supratherapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin 250 mg 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: Antiinfectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones

ATC code: J01MA12

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

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

**PK/PD relationship**

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

**Mechanism of resistance**

The main mechanism of resistance arises through stepwise mutations in the coding regions of the gyrase subunits (gyrA and gyrB) and DNA topoisomerase IV (parC). Accumulation of mutations in several of these genes increases the MIC in a stepwise manner. Low-level resistance to fluoroquinolones may also arise through changes in membrane porins or from genes regulating the activity of efflux pumps, resulting in lower membrane permeability and higher efflux, respectively. A plasmid-mediated resistance mechanism, protecting DNA from quinolone binding, has been observed.

**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 (2006-06-20):**

<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> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> ¹</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Streptococcus</em> A,B,C,G</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M. catarrhalis</em> ²</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td>Non-species related breakpoints ³</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
</tbody>
</table>

¹ The S/I-breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints relate to high dose therapy.

² Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.

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

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

COMMONLY SUSCEPTIBLE MICROORGANISMS

Aerobic Gram-positive bacteria

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

Aerobic Gram-negative bacteria

*Haemophilus influenzae* *
*Haemophilus para-influenzae* *
*Klebsiella oxytoca*
*Klebsiella pneumoniae* *
*Moraxella catarrhalis* *
*Pasteurella multocida*
*Proteus vulgaris*
*Providencia rettgeri*

Anaerobic bacteria

*Peptostreptococcus*

Other

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

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive bacteria

*Enterococcus faecalis* *
*Staphylococcus aureus* methicillin-resistant
*Staphylococcus haemolyticus* methicillin-resistant

Aerobic Gram-negative bacteria

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

**Anaerobic bacteria**
- *Bacteroides fragilis*
- *Bacteroides ovatus*
- *Bacteroides thetaiotamicron*
- *Bacteroides vulgatus*
- *Clostridium difficile*

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

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

### 5.2 Pharmacokinetic properties

#### Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is approximately 100%. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

Food has little effect on the absorption of levofloxacin.

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

#### Penetration into tissues and body fluids:

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

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>ClR [ml/min]</th>
<th>&lt;20</th>
<th>20-40</th>
<th>50-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clk [ml/min]</td>
<td>13</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>t½ [h]</td>
<td>35</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

Elderly 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 (LD<sub>50</sub>) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg. Administration of 500 mg/kg p.o. to monkeys induced little effect apart from vomiting.

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

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

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

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

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

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Levofloxacin 250 mg film-coated tablets contain the following excipients:

<i>Tablet core:</i>
Crospovidone (E1202)
Hypermellose (E464)
Microcrystalline cellulose (E460)
Talc (E553B)
Magnesium stearate (E470b)

Tablet coating:
Hypermellose (E464)
Titanium dioxide (E 171)
Talc (E553B)
Macrogol
Iron oxide yellow (E 172)
Iron oxide red (E 172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

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

6.5 Nature and contents of container
PVC aluminium blisters containing film-coated tablets.
Pack sizes: 7, 10 or 50.

6.6 Special precautions for disposal
A score line allows adaptation of the dose in patients with impaired renal function.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 - Block C
9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
Levofloxacin 250 mg film-coated tablets: PL 19156/0045.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/11/2009

10 DATE OF REVISION OF THE TEXT
25/11/2009
LEVOFLOXACIN 500G FILM-COATED TABLETS
PL 19156/0046

SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet of Levofloxacin 500 mg contains 500 mg of levofloxacin as active substance corresponding to 512.46 mg of levofloxacin hemihydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Levofloxacin 500 mg film-coated tablets:
Light peach coloured film-coated tablets scored on both sides and debossed with “J” and “500” on either side of the scoreline on one side of the tablet.

The tablet can be divided in two equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults with infection of mild or moderate severity levofloxacin 500 mg is indicated for the treatment of the following infections when due to levofloxacin-susceptible micro-organisms:
- Acute sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Community-acquired pneumonia
- 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
Levofloxacin 500 mg is administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

Duration of treatment
The duration of treatment varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin 500 mg should be continued for a minimum of 48 to 72 hours after the patient has become a febrile or evidence of bacterial eradication has been obtained.

Method of administration
Levofloxacin 500 mg should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals. Levofloxacin 500 mg should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

**Posology**
The following dose recommendations can be given for Levofloxacin 500 mg:

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Daily dose regimen (according to severity)</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute sinusitis</td>
<td>500 mg once daily</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Acute exacerbations of chronic bronchitis</td>
<td>250 to 500 mg once daily</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>500 mg once 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 $\leq$ 50 ml/min)

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

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

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

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

**In children**
Levofloxacin 500 mg is contraindicated in children and growing adolescents (see section 4.3).

### 4.3 Contraindications
Levofloxacin 500 mg must not be used:
- in patients hypersensitive to levofloxacin or other quinolones or any of the excipients,
- in patients with epilepsy,
• in patients with history of tendon disorders related to fluoroquinolone administration,
• in children or growing adolescents,
• during pregnancy,
• in breast-feeding women.

4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia Levofloxacin 500 mg may not be the optimal therapy.

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

**Tendinitis and tendon rupture**

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Levofloxacin 500 mg. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin 500 mg 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 500 mg, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Levofloxacin 500 mg must be stopped immediately and patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

**Patients predisposed to seizures**

Levofloxacin 500 mg is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system 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 500 mg 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 in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

**Psychotic reactions**

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

**QT interval prolongation**

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome,
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides),
- uncorrected electrolyte imbalance (e.g. 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 method.

**Hepatobiliary disorders**

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

**Methicillin-resistant Staphylococcus aureus (MRSA):**

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

4.5 Interaction with other medicinal products and other forms of interaction

**Effect of other medicinal products on Levofloxacin 500 mg**

*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 500 mg. 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 500 mg administration (see section 4.2). No interaction was found with calcium carbonate.

*Sucralfate*

The bioavailability of Levofloxacin 500 mg is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levofloxacin 500 mg, it is best to administer sucralfate 2 hours after the Levofloxacin 500 mg administration (see section 4.2).

*Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs*

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

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

*Probenecid and cimetidine*

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

**Other relevant information**

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

**Effect of Levofloxacin 500 mg 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 500 mg may therefore be administered regardless of food intake.

4.6 **Pregnancy and lactation**

**Pregnancy**

Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin 500 mg must not be used in pregnant women.

**Lactation**

In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin 500 mg must not be used in breast-feeding women.

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

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

4.8 **Undesirable effects**

The information given below is based on data from clinical studies in more than 5,000 patients and on extensive post-marketing experience.
The adverse reactions are described according to the MedDRA system organ class below. Frequencies are defined using the following convention:

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

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

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

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Leukopenia, eosinophilia</td>
</tr>
<tr>
<td>Rare</td>
<td>Thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Not Known</td>
<td>Pancytopenia, haemolytic anaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td>Rare</td>
<td>Convulsion, tremor, paraesthesia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Diarrhoea, nausea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vomiting, abdominal pain, dyspepsia, flatulence, constipation</td>
</tr>
<tr>
<td>Rare</td>
<td>Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td>Very rare</td>
<td>Renal failure acute (e.g. due to nephritis interstitial)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Rash, pruritus</td>
</tr>
<tr>
<td>Rare</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Very rare</td>
<td>Angioneurotic oedema, photosensitivity reaction</td>
</tr>
<tr>
<td>Not Known</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis. Muco-cutaneous reactions may sometimes occur even after the first dose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Tendon rupture (see section 4.4). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with</td>
</tr>
</tbody>
</table>
myasthenia gravis
Not Known Rhabdomyolysis

**Metabolism and nutrition disorders**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Hypoglycaemia, particularly in diabetic patients (see section 4.4)</td>
</tr>
</tbody>
</table>

**Infections and infestations**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Fungal infection (and proliferation of other resistant microorganisms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>

**Vascular disorders**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Asthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Pyrexia</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Asthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Not Known</td>
<td>Pain (including pain in back, chest, and extremities)</td>
</tr>
</tbody>
</table>

**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) |

**Hepatobiliary disorders**

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

**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), hallucinations |

Other undesirable effects, which have been associated with fluoroquinolone administration, include:

- Extrapyramidal symptoms and other disorders of muscular coordination
- Hypersensitivity vasculitis
- Attacks of porphyria in patients with porphyria.

### 4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin 500 mg 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: Antifectives for systemic use – Antibacterials for systemic use – Quinolone antibacterials – Fluoroquinolones

ATC code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.
Mechanism of action
As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance
The main mechanism of resistance arises through stepwise mutations in the coding regions of the gyrase subunits (gyrA and gyrB) and DNA topoisomerase IV (parC). Accumulation of mutations in several of these genes increases the MIC in a stepwise manner. Low-level resistance to fluoroquinolones may also arise through changes in membrane porins or from genes regulating the activity of efflux pumps, resulting in lower membrane permeability and higher efflux, respectively. A plasmid-mediated resistance mechanism, protecting DNA from quinolone binding, has been observed.

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 (2006-06-20):**

<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> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> ¹</td>
<td>≤2 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>Streptococcus</em> A,B,C,G</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>≤1 mg/L</td>
<td>&gt;1 mg/L</td>
</tr>
<tr>
<td><em>M. catarrhalis</em> ²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-species related breakpoints ³</td>
<td>≤1 mg/L</td>
<td>&gt;2 mg/L</td>
</tr>
</tbody>
</table>

¹ The S/I-breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints relate to high dose therapy.

² Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.

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

**Antibacterial spectrum**

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

**COMMONLY SUSCEPTIBLE MICROORGANISMS**

**Aerobic Gram-positive bacteria**

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

**Aerobic Gram-negative bacteria**

*Haemophilus influenzae*  
*Haemophilus para-influenzae*  
*Klebsiella oxytoca*  
*Klebsiella pneumoniae*  
*Moraxella catarrhalis*  
*Pasteurella multocida*  
*Proteus vulgaris*  
*Providencia rettgeri*  

**Anaerobic bacteria**

*Peptostreptococcus*  

**Other**

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

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

**Aerobic Gram-positive bacteria**

*Enterococcus faecalis*  
*Staphylococcus aureus* methicillin-resistant  
*Staphylococcus haemolyticus* methicillin-resistant  

**Aerobic Gram-negative bacteria**

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

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

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

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

5.2 Pharmacokinetic properties
Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is approximately 100%. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.
Food has little effect on the absorption of levofloxacin.

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

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

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

**Penetration into Blister Fluid**

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

**Penetration into Cerebro-Spinal Fluid**

Levofloxacin has poor penetration into cerebro-spinal fluid.

**Penetration into prostatic tissue**

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

**Concentration in urine**

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

**Metabolism**

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

**Elimination**

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

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

**Subjects with renal insufficiency**

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

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

**Elderly 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, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey. Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The No Observed Adverse Effect Levels (NOELs) in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively.

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

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

Reproductive toxicity

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

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 30 mg/kg/day or intravenously with up to 25 mg/kg/day.

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

Genotoxicity

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

Phototoxic potential

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

Carcinogenic potential

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

Toxicity to joints

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

6.1 List of excipients
Levofloxacin 500 mg film-coated tablets contain the following excipients:

**Tablet core:**
- Crospovidone (E1202)
- Hypromellose (E464)
- Microcrystalline cellulose (E460)
- Talc (E553B)
- Magnesium stearate (E470b)

**Tablet coating:**
- Hypromellose (E464)
- Titanium dioxide (E 171)
- Talc (E553B)
- Macrogol
- Iron oxide yellow (E 172)
- Iron oxide red (E 172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

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

6.5 Nature and contents of container
PVC aluminium blisters containing film-coated tablets.
Pack sizes: 7, 10 or 50.

6.6 Special precautions for disposal
A score line allows adaptation of the dose in patients with impaired renal function.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 - Block C
9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
Levofloxacin 500 mg film-coated tablets: PL 19156/0046.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/11/2009

10 DATE OF REVISION OF THE TEXT
25/11/2009
PATIENT INFORMATION LEAFLET

LEVOFLOXACIN 2500G AND 500MG FILM-COATED TABLETS
PL 19156/0045-46

PACKAGE LEAFLET INFORMATION FOR THE USER

Levofloxacin 250 mg film-coated tablets

Levofloxacin 500 mg film-coated tablets

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, use your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- Even if you feel symptom-free the same applies.

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

1. WHAT LEVOFLOXACIN FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Levofloxacin 250-500mg film-coated tablets. Levofloxacin film-coated tablets contain a medicine called levofloxacin. This belongs to a group of medicines called antibiotics. Levofloxacin is a "quinoline" antibiotic. It works by killing the bacteria that cause infections in your body.

Levofloxacin film-coated tablets can be used to treat infections of the:
- Sinuses.
- Lungs, in people with long-term breathing problems or pneumonia.
- Urinary tract, including your kidneys or bladder.
- Pre-ear gadget, where you have a long-lasting infection.
- Skin and subcutaneous tissues. This is sometimes called soft tissue.

2. BEFORE YOU TAKE LEVOFLOXACIN FILM-COATED TABLETS

Do not take this medicine and do not drive your car:
- If you are allergic to levofloxacin, any other quinolone antibiotic such as norfloxacin, ofloxacin or any of the ingredients of Levofloxacin film-coated tablets (listed in Section 6 below).
- If you have an allergy to antibiotics in general.
- If you have had a previous infection with a fungus that was related to treatment with a "quinoline" antibiotic. A fungus is a type of organisms that can grow in your mouth and on your skin.
- If you are pregnant or you are breast-feeding.

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

Take special care with Levofloxacin film-coated tablets

Check with your doctor or pharmacist before taking this medicine:
- If you are 65 years of age or older.
- If you are using corticosteroids, sometimes called steroids (e.g. "taking other medicines" below).
- You have ever had a fit (seizure).
- You have ever had a bad stomach ulcer.
- You have heart problems.
- You have ever been told you have diabetes.
- You have ever had liver problems.
- You have had a seizure before.
- You have had a severe allergic reaction to this medicine.

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

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have been recently taking any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Levofloxacin film-coated tablets can affect the way some other medicines work. Also some medicines can affect the way Levofloxacin film-coated tablets work.

In particular, tell your doctor if you are taking any of the following medicines. This is because it may increase the chance of you getting side effects, when taken with Levofloxacin film-coated tablets:
- Corticosteroids, sometimes called steroids - used for inflammation. You may be more likely to have inflammation and/or breaking 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.
- Theobromines - used for breathing problems. You are more likely to have a fit (seizure) if taken with Levofloxacin film-coated tablets.
- Non-steroidal anti-inflammatory drugs (NSAIDs) - used for pain and inflammation such as aspirin, ibuprofen, ketoprofen, diclofenac and indomethacin. You are more likely to have a fit (seizure) if taken with Levofloxacin film-coated tablets.
- Opioids - used for strong painkillers called "opiates" in people taking Levofloxacin film-coated tablets. If your doctor is due to take a tetra bid, tell them you are taking Levofloxacin film-coated tablets.

3. HOW TO TAKE LEVOFLOXACIN FILM-COATED TABLETS

Always take Levofloxacin film-coated 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.

Prevent your skin from sunlight:
Keep out of direct sunlight while taking this medicine. Because this is a very short life it will become much more sensitive to the sun and may burn, tingle or severely blister if you do not take the following precautions:
- Make sure you are high factor sun cream.
- Always wear a hat and sunglasses which cover your arms and legs.
- Avoid sun beds.

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

How much to take
- Your doctor will decide on how many Levofloxacin film-coated tablets you should take.
- This 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 have had an effect of your medicine is too weak or strong, do not change the dose yourself, but ask your doctor.

Adults and the elderly
- Infections of the sinuses:
  - One tablet of Levofloxacin 250 mg, once a day.
  - Or one tablet of Levofloxacin 500 mg, once a day.
- Infections of the lungs, in people with long-term breathing problems:
  - One tablet of Levofloxacin 250 mg, once a day.
  - Or, one tablet of Levofloxacin 500 mg, once a day.
- Infections of the urinary tract, including your kidneys or bladder:
  - One tablet of Levofloxacin 250 mg, once a day.
  - Or, one tablet of Levofloxacin 500 mg, once a day.
- Infections of the skin and subcutaneous tissues, including infections of the skin and subcutaneous tissues, including:?.
  - Two tablets of Levofloxacin 250 mg, once a day.
  - Or, two tablets of Levofloxacin 500 mg, once a day.
- Infections of the skin and subcutaneous tissues, including:
  - Two tablets of Levofloxacin 500 mg, once a day.
  - Or, one tablet of Levofloxacin 500 mg, once a day.

Children and teenagers:
This medicine may not be given to children or teenagers.

MHRA-UKPAR – Levofloxacin 250mg & 500mg Film Coated Tablets
PL 19156/0045-46 - 47 -
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: convulsions, fever, dizziness, eye problems, tremors, muscle pains, liver problems, memory loss, and kidney problems. You may also become more sensitive to sunlight or other forms of light. 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 250mg - 500mg can cause side effects, although not everybody gets them. These effects are normally mild or moderate and often disappear after a short time.

Stop taking Levofloxacin 250mg - 500mg and see a doctor or go to a hospital straight away if you notice the following side effects:

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

Stop taking Levofloxacin 250mg - 500mg and see a doctor straight away if you notice any of the following severe side effects - you may need urgent medical treatment:

Rare effects (less than 1 person in 100):
- Unusual vision changes which may involve blurring or swelling of the skin around your eyes, nose, and mouth.
- Loss of appetite, skin and eyes becoming yellow or yellowish, dark-colored urine, itching, or tender stomach (abdomen). These may be signs of liver problems.

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

Common effects (less than 1 person in 10):
- Feeling sick (nausea) and diarrhoea.
- Increase in the level of some liver enzymes in your blood.

Uncommon effects (less than 1 person in 100):
- Feeling and skin rash.
- Loss of appetite, stomach upset or indigestion (upset stomach), being sick (vomiting) or pain in your stomach area, being bloated (distension) or constipation.
- Insomnia, feeling nervous, 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.
- The number of other bacteria in some parts of the body may increase, which may need to be treated.

Rare effects (less than 1 person in 100):
- Tingling in your hands and feet (parasthesia) or breathing.
- Feeling stressed (anxiety), depressed, mental problems, feeling restless (agitation) or feeling unusual.
- Unusual fast beating of your heart or low blood pressure.
- Joint pain or muscle pain.
- Blurred or dimming of vision due to a swelling in the number of blood platelets.
- Low number of white blood cells (leucopenia).
- Difficulty breathing or wheezing (bronchospasm).
- Difficulty swallowing (dysphagia).
- Swelling of the legs (oedema).

Very rare effects (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 eye sight or changes in the way things taste and smell.
- Seizing or having 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 consciousness (unconsciousness) like a knock.
- Muscle weakness. This is important for people with myasthenia gravis (a rare disease of the nervous system).
- Inflammation of the liver, changes in the way your liver 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.

Other side effects include:
- Rash 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 (haemolytic anemia).
- Feeling too hot (hyperthermia).
- Pain, including pain in the back, chest and abdomen.
- Problems sleeping and waking.
- Attack of porphyria in people who already have porphyria (a very rare metabolic disease).
- Infection of your tubes that carry blood around your body (vessel) due to an allergic reaction.

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

5. HOW TO STORE LEVOFLAXIN FILM-COATED TABLETS

Keep out of the reach and sight of children.

This medicine does not require any special storage conditions but it is best to keep Levofloxacin film-coated tablets in the original strips and box in a dry place.

Do not use Levofloxacin film-coated tablets after the expiry date (EXP) which is stated on the carton and box.

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

The active ingredient is levofloxacin. Each tablet of Levofloxacin 250mg tablets contains 250 mg of levofloxacin and each tablet of Levofloxacin 500mg tablets contains 500 mg of levofloxacin.

The other ingredients are:
- For the tablet core: croscarmellose sodium (E403), sodium starch glycolate (E423), magnesium stearate (E473).
- For the tablet coating: hypromellose (E404), titanium dioxide (E171), talc (E901), microcrystalline cellulose (E900), iron oxide yellow (E172) and iron oxide red (E172).

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

Levofloxacin 250mg film-coated tablets are light pink coloured, film-coated tablets, scored on both sides and debossed with “J” and “200” on either side of the score line on one side of tablet.

Levofloxacin 500mg film-coated tablets are light pink coloured, film-coated tablets, scored on both sides and debossed with “J” and “500” on either side of the score line on one side of tablet.

The tablets can be identified in two equal halves.

The tablets are packaged in pack sizes of 7, 10 and 50 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Jubilant Life Science Limited

Marketing Authorisation Holder

Jubilant Life Science Limited

Manufacturer

Pill supply

Jubilant Life Science Limited

Manufacturer

Jubilant Life Science Limited

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last updated on 08/06/20.
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**{carton box}**

### 1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin 250 mg film-coated tablets

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains levofloxacin hemihydrate equivalent to 250 mg levofloxacin

### 3. LIST OF EXCIPIENTS

/ 

### 4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets  
10 film-coated tablets  
50 film-coated tablets

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.  
Oral use

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

Keep out of the reach and sight of children.

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

/ 

### 8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

/

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

/

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

PL 19156/0045

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

/

16. INFORMATION IN BRAILLE

levofloxacin 250 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin 250 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jubilant Pharmaceuticals nv

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

/

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin 500 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains levofloxacin hemihydrate equivalent to 500 mg levofloxacin

3. LIST OF EXCIPIENTS

/
4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
10 film-coated tablets
50 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the reach and sight of children.

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
/

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14. GENERAL CLASSIFICATION FOR SUPPLY

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15. INSTRUCTIONS ON USE

/

16. INFORMATION IN BRAILLE

levofloxacin 500 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin 500 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORITY

Jubilant Pharmaceuticals nv

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

/