CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020634/S04 and 020635/S03

FINAL PRINTED LABELING
LEVOFLOXACIN TABLET

DESCRIPTION

LEVAQUIN™ (levofloxacin tablets) Tablets contain levofloxacin, a synthetic broad spectrum antibacterial agent for oral administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(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.

The chemical structure is:

![Chemical Structure](image)

Its empirical formula is C_{18}H_{20}F_{1}N_{3}O_{4} \cdot \frac{1}{2} H_{2}O and its molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered soluble to freely soluble in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered freely soluble in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: Al^{3+} > Cu^{2+} > Zn^{2+} > Mg^{2+} > Ca^{2+}.

LEVAQUIN Tablets are available as film-coated tablets and contain the following inactive ingredients:

250-mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

500-mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose,
crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.

CLINICAL PHARMACOLOGY

Absorption
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500-mg oral dose of levofloxacin is approximately 99%. Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral dosing regimens. Steady-state is reached within 48 hours following a 500-mg once-daily regimen. The peak and trough plasma concentrations attained following multiple once-daily oral 500-mg regimens were approximately 5.7 and 0.5 μg/mL, respectively.

Oral administration with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin can be administered without regard to food.

The plasma concentration profile of levofloxacin after i.v. administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and i.v. routes of administration can be considered interchangeable. (See following chart.)

![Mean Levofloxacin Plasma Concentration-Time Profiles](image)

Distribution
The mean volume of distribution of levofloxacin generally ranges from 89 to 112 L after single and multiple 500-mg doses, indicating widespread distribution into body tissues. Penetration of levofloxacin into blister fluid is rapid and extensive. The blister fluid to plasma AUC ratio is approximately 1. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations
were generally 2- to 5-fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 μg/g over a 24-hour period after a single 500-mg oral dose.

*In vitro*, over a clinically relevant range (1 to 10 μg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

**Metabolism**
Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacín. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. 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.

**Excretion**
Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

**Special Populations**

**Geriatric**
There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects’ differences in creatinine clearance are taken into consideration. Following a 500-mg oral dose of levofloxacin to healthy elderly subjects (66-80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.
Pediatric
The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender
There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500-mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race
The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 nonwhite. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal insufficiency
Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in patients with impaired renal function (creatinine clearance \(\leq 80\) mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.)

Hepatic insufficiency
Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial infection
The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-drug interactions
The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See PRECAUTIONS: Drug Interactions.)

The mean (± SD) pharmacokinetic parameters of levofloxacin determined
under single and steady state conditions following oral (p.o.) or intravenous (i.v.) doses of levofloxacin are summarized as follows:
### BEST POSSIBLE COPY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>(C_{\text{max}}) ((\mu\text{g/mL}))</th>
<th>(T_{\text{max}}) (h)</th>
<th>AUC ((\mu\text{g} \cdot \text{h/mL}))</th>
<th>(\text{CL/F}) (mL/min)</th>
<th>(\text{Vd/F}) (L)</th>
<th>(t_{\text{1/2}}) (h)</th>
<th>(\text{CL}_R) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg p.o.</td>
<td>2.8 ± 0.4</td>
<td>1.6 ± 1.0</td>
<td>27.2 ± 3.9</td>
<td>156 ± 20</td>
<td>ND</td>
<td>7.3 ± 0.9</td>
<td>142 ± 21</td>
</tr>
<tr>
<td>500 mg p.o.</td>
<td>5.1 ± 0.8</td>
<td>1.3 ± 0.6</td>
<td>47.9 ± 6.8</td>
<td>178 ± 28</td>
<td>ND</td>
<td>6.3 ± 0.6</td>
<td>103 ± 30</td>
</tr>
<tr>
<td>500 mg i.v.</td>
<td>6.2 ± 1.0</td>
<td>1.0 ± 0.1</td>
<td>48.3 ± 5.4</td>
<td>175 ± 20</td>
<td>90 ± 11</td>
<td>6.4 ± 0.7</td>
<td>112 ± 25</td>
</tr>
</tbody>
</table>

| Multiple dose | | | | | | | |
| 500 mg q24h p.o. | 5.7 ± 1.4 | 1.1 ± 0.4 | 47.5 ± 6.7 | 175 ± 25 | 102 ± 22 | 7.6 ± 1.6 | 116 ± 31 |
| 500 mg q24h i.v. | 6.4 ± 0.8 | ND | 54.6 ± 11.1 | 158 ± 29 | 91 ± 12 | 7.0 ± 0.8 | 99 ± 28 |
| 500 mg or 250 mg q24h i.v., patients with bacterial infection | 8.7 ± 4.0 | ND | 72.5 ± 51.2 | 154 ± 72 | 111 ± 58 | ND | ND |

#### 500 mg p.o. single dose, effects of gender and age:

<table>
<thead>
<tr>
<th>Gender</th>
<th>(C_{\text{max}}) ((\mu\text{g/mL}))</th>
<th>(T_{\text{max}}) (h)</th>
<th>AUC ((\mu\text{g} \cdot \text{h/mL}))</th>
<th>(\text{CL/F}) (mL/min)</th>
<th>(\text{Vd/F}) (L)</th>
<th>(t_{\text{1/2}}) (h)</th>
<th>(\text{CL}_R) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>5.5 ± 1.1</td>
<td>1.2 ± 0.4</td>
<td>54.4 ± 18.9</td>
<td>166 ± 44</td>
<td>89 ± 13</td>
<td>7.5 ± 2.1</td>
<td>126 ± 38</td>
</tr>
<tr>
<td>female</td>
<td>7.0 ± 1.6</td>
<td>1.7 ± 0.5</td>
<td>67.7 ± 24.2</td>
<td>136 ± 44</td>
<td>62 ± 16</td>
<td>6.1 ± 0.8</td>
<td>106 ± 40</td>
</tr>
<tr>
<td>young</td>
<td>5.5 ± 1.0</td>
<td>1.5 ± 0.6</td>
<td>47.5 ± 9.8</td>
<td>182 ± 35</td>
<td>83 ± 18</td>
<td>6.0 ± 0.9</td>
<td>140 ± 33</td>
</tr>
<tr>
<td>elderly</td>
<td>7.0 ± 1.6</td>
<td>1.4 ± 0.5</td>
<td>74.7 ± 23.3</td>
<td>121 ± 33</td>
<td>67 ± 19</td>
<td>7.6 ± 2.0</td>
<td>91 ± 29</td>
</tr>
</tbody>
</table>

#### 500 mg p.o. single dose, patients with renal insufficiency:

<table>
<thead>
<tr>
<th>(\text{CL}_{\text{CR}})</th>
<th>(C_{\text{max}}) ((\mu\text{g/mL}))</th>
<th>(T_{\text{max}}) (h)</th>
<th>AUC ((\mu\text{g} \cdot \text{h/mL}))</th>
<th>(\text{CL/F}) (mL/min)</th>
<th>(\text{Vd/F}) (L)</th>
<th>(t_{\text{1/2}}) (h)</th>
<th>(\text{CL}_R) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-80 mL/min</td>
<td>7.5 ± 1.8</td>
<td>1.5 ± 0.5</td>
<td>95.6 ± 11.8</td>
<td>88 ± 10</td>
<td>ND</td>
<td>9.1 ± 0.9</td>
<td>57 ± 8</td>
</tr>
<tr>
<td>20-49 mL/min</td>
<td>7.1 ± 3.1</td>
<td>2.1 ± 1.3</td>
<td>182.1 ± 62.6</td>
<td>51 ± 19</td>
<td>ND</td>
<td>27 ± 10</td>
<td>26 ± 13</td>
</tr>
<tr>
<td>&lt;20 mL/min</td>
<td>8.2 ± 2.6</td>
<td>1.1 ± 1.0</td>
<td>263.5 ± 72.5</td>
<td>33 ± 8</td>
<td>ND</td>
<td>35 ± 5</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>hemodialysis</td>
<td>5.7 ± 1.0</td>
<td>2.8 ± 2.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>76 ± 42</td>
<td>ND</td>
</tr>
<tr>
<td>CAPD</td>
<td>6.9 ± 2.3</td>
<td>1.4 ± 1.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>51 ± 24</td>
<td>ND</td>
</tr>
</tbody>
</table>

1 clearance/bioavailability
2 volume of distribution/bioavailability
3 healthy males 18-53 years of age
4 500 mg q48h for patients with moderate renal impairment (\(\text{CL}_{\text{CR}}\) 20-50 mL/min) and infections of the respiratory tract or skin
5 dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modelling
6 healthy males 22-75 years of age
7 healthy females 18-80 years of age
8 young healthy male and female subjects 18-38 years of age
9 healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; \(F = 0.99 ± 0.08\); ND = not determined.
MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones differ in chemical structure and mode of action from β-lactam antibiotics. Fluoroquinolones may, therefore, be active against bacteria resistant to β-lactam antibiotics.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: $10^{-9}$ to $10^{-10}$). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

**Aerobic gram-positive microorganisms**
- *Enterococcus faecalis*
- *Staphylococcus aureus*
- *Staphylococcus saprophyticus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

**Aerobic gram-negative microorganisms**
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*
- *Legionella pneumophila*
- *Moraxella catarrhalis*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

**Other microorganisms**
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*
The following in vitro data are available, but their clinical significance is unknown.

Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC's) of 2µg/mL or less against most strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

**Aerobic gram-positive microorganisms**
- *Staphylococcus epidermidis*
- *Streptococcus* (Group C/F)
- *Streptococcus* (Group G)
- *Streptococcus agalactiae*
- *Viridans group streptococci*

**Aerobic gram-negative microorganisms**
- *Acinetobacter anitratus*
- *Acinetobacter baumannii*
- *Acinetobacter calcoaceticus*
- *Acinetobacter Iwoffii*
- *Bordetella pertussis*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Enterobacter aerogenes*
- *Enterobacter agglomerans*
- *Enterobacter sakazakii*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Pseudomonas fluorescens*
- *Serratia marcescens*

**Anaerobic gram-positive microorganisms**
- *Clostridium perfringens*

**Susceptibility Tests**

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity. However, until levofloxacin susceptibility testing is available, the susceptibility of the organism to ofloxacin may be used to predict susceptibility to levofloxacin. While ofloxacin susceptible organisms will be susceptible to levofloxacin, ofloxacin intermediate or resistant organisms may be susceptible to levofloxacin.

**Dilution techniques:**

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of
bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method\(^1\) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*:

<table>
<thead>
<tr>
<th>MIC ((\mu g/mL))</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;2)</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>(\geq8)</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:\(^a\)

<table>
<thead>
<tr>
<th>MIC ((\mu g/mL))</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;2)</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

\(^a\)These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.\(^1\)

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*:\(^b\)

<table>
<thead>
<tr>
<th>MIC ((\mu g/mL))</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;2)</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>(\geq8)</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

\(^b\)These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in
interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>ATCC</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>29212</td>
<td>0.25 - 2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25922</td>
<td>0.008 - 0.06</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>35218</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>27853</td>
<td>0.5 - 4</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>29213</td>
<td>0.06 - 0.5</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>49247</td>
<td>0.008 - 0.03</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>49619</td>
<td>0.5 - 2</td>
</tr>
</tbody>
</table>

*This quality control range is applicable to only H. influenzae ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).*

*This quality control range is applicable to only S. pneumoniae ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

**Diffusion techniques:**

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For aerobic microorganisms other than Haemophilus influenzae, Haemophilus parainfluenzae, and Streptococcus pneumoniae:

<table>
<thead>
<tr>
<th>Zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥17</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>14-16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤13</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For Haemophilus influenzae and Haemophilus parainfluenzae:*
Zone diameter (mm) | Interpretation
---|---
≥17 | Susceptible (S)

*These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.2*

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus pneumoniae*:4

<table>
<thead>
<tr>
<th>Zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥17</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>14-16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤13</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*These zone diameter standards for *Streptococcus pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>ATCC 25923</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>ATCC 49247&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>ATCC 49619&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).2

<sup>b</sup>This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO₂.
INDICATIONS AND USAGE

LEVANQUIN Tablets are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis.

Acute bacterial exacerbation of chronic bronchitis due to Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis.

Community-acquired pneumonia due to Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae. (See CLINICAL STUDIES.)

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to Staphylococcus aureus, or Streptococcus pyogenes.

Complicated urinary tract infections (mild to moderate) due to Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, or Pseudomonas aeruginosa.

Acute pyelonephritis (mild to moderate) caused by Escherichia coli.

Uncomplicated urinary tract infections (mild to moderate) due to, Escherichia coli, Klebsiella pneumoniae, or Staphylococcus saprophyticus.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with a history of hypersensitivity to
levofloxacin, quinolone antimicrobial agents, or any other components of this product.

WARNINGS

THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)

Serious and sometimes fatal events, some due to hypersensitivity, and some
due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile colitis. (See ADVERSE REACTIONS.)

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General:
Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency.
Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance ≤80 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See WARNINGS and Drug Interactions.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately. (See Drug Interactions and ADVERSE REACTIONS.)

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See WARNINGS and ADVERSE REACTIONS.)

Information for Patients:
Patients should be advised:
• to drink fluids liberally;
• that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multi-vitamin preparations with zinc should be taken at least two hours before or two hours after levofloxacin administration. (See Drug Interactions);
• that levofloxacin can be taken without regard to meals;
• that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See WARNINGS and ADVERSE REACTIONS);
• to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise
until the diagnosis of tendinitis or tendon rupture has been confidently excluded;

- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See WARNINGS and ADVERSE REACTIONS);

- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;

- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician. (See PRECAUTIONS: General and Drug Interactions.)

**Drug Interactions:**

Antacids, Sucralfate, Metal Cations, Multi-Vitamins: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multi-vitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

Theophylline: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See WARNINGS and PRECAUTIONS: General.)

Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S-warfarin was detected in a clinical study involving healthy volunteers. No significant change in prothrombin time was noted in the presence of levofloxacin. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, since some quinolones have been reported to enhance the effects of oral anticoagulant warfarin or its derivatives in the patient population, the prothrombin time or other suitable coagulation test
should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin $C_{\text{max}}$ and $k_{\text{s}}$ were slightly lower while $T_{\text{max}}$ and $t_{\frac{1}{2}}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{\frac{1}{2}}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and $CL_{R}$ were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See WARNINGS and PRECAUTIONS: General.)

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years; the highest dose was 2 or 10 times the recommended human dose based on surface area or body weight, respectively.

Levofloxacin was not mutagenic in the following assays; Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/HGPRT forward mutation
assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day (2124 mg/m²), corresponding to 3.0 or 18 times the recommended maximum human dose based on surface area or body weight, respectively, and intravenous doses as high as 100 mg/kg/day (590 mg/m²), corresponding to 1.0 or 5 times the recommended maximum human dose based on surface area or body weight, respectively.

Pregnancy: Teratogenic Effects. Pregnancy Category C.
Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day (4779 mg/m²), which corresponds to 14 or 82 times the recommended maximum human dose based on surface area or body weight, respectively, or at intravenous doses as high as 160 mg/kg/day (944 mg/m²) corresponding to 2.7 or 16 times the recommended maximum human dose based on surface area or body weight, respectively. Doses equivalent to 26 or 81 times the recommended maximum human dose of levofloxacin (based on surface area or body weight, respectively) caused decreased fetal body weight and increased fetal mortality in rats when administered orally at 810 mg/kg/day (8910 mg/m²). No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day (550 mg/m²) which corresponds to 1.6 or 5.0 times the recommended maximum human dose based on surface area or body weight, respectively, or when dosed intravenously as high as 25 mg/kg/day (275 mg/m²), corresponding to 0.8 or 2.5 times the maximum recommended human dose based on surface area or body weight, respectively.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

Nursing Mothers:
Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in children and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNINGS.)

ADVERSE REACTIONS
The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving levofloxacin therapy, 3.4% discontinued levofloxacin therapy due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:
- nausea 1.3%, diarrhea 1.1%, vaginitis 0.7%, pruritus 0.5%, abdominal pain 0.4%, dizziness 0.4%, flatulence 0.4%, rash 0.4%, dyspepsia 0.3%, genital moniliasis 0.3%, insomnia 0.3%, taste perversion 0.2%, vomiting 0.2%, anorexia 0.1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, fungal infection 0.1%, headache 0.1%, increased sweating 0.1%, leukorrhea 0.1%, malaise 0.1%, nervousness 0.1%, sleep disorders 0.1%, tremor 0.1%, urticaria 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:
- nausea 7.1%, headache 6.4%, diarrhea 5.6%, insomnia 4.0%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:
- constipation 2.9%, dizziness 2.9%, abdominal pain 2.6%, dyspepsia 2.5%, vomiting 2.2%, rash 1.7%, flatulence 1.6%, vaginitis 1.6%, pruritus 1.5%, fatigue 1.3%, back pain 1.2%, pain 1.2%, chest pain 1.1%, pharyngitis 1.1%, rhinitis 1.1%, taste perversion 1.0%.

In clinical trials, the following events occurred in 0.5 to less than 1% of patients, regardless of drug relationship:
- anorexia, anxiety, arthralgia, coughing, dry mouth, dyspnea, ear disorder (not otherwise specified), edema, fever, fungal infection, genital pruritus, increased sweating, skin disorder, somnolence.

In clinical trials, the following events, of potential medical importance, occurred at a rate of less than 0.5% regardless of drug relationship:
- abnormal coordination, abnormal dreaming, abnormal hepatic function, abnormal platelets, abnormal renal function, abnormal vision, acute renal failure, aggravated diabetes mellitus, aggressive reaction, agitation, anemia, angina pectoris, ARDS, arrhythmia, arthritis, arthrosis, asthenia, asthma, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, carcinoma, cerebrovascular disorder, cholelithiasis, circulatory failure, coma, confusion, conjunctivitis, convulsions (seizures), coronary thrombosis, dehydration, delirium, depression, diplopia, dysphagia, ejaculation failure, embolism (blood clot), emotional lability, epistaxis, erythema nodosum, face edema, gastroenteritis, genital moniliasis, G.I. hemorrhage, granulocytopenia, haematuria, haemoptysis, hallucination, heart block, hepatic coma, hyperglycaemia, hyperkalaemia, hyperkinesia, hypertension, hypertonia, hypoaesthesia, hypoglycemia, hypokalaemia, hypotension, hypoxia, impaired
concentration, impotence, increased LDH, involuntary muscle contractions, jaundice, leukocytosis, leukopenia, lymphadenopathy, malaise, manic reaction, mental deficiency, muscle weakness, myalgia, myocardial infarction, nervousness, palpitation, pancreatitis, paraesthesia, paralysis, paranoia, parosmia, phlebitis, pleural effusion, postural hypotension, pseudomembranous colitis, purpura, respiratory insufficiency, rhabdomyolysis, rigors, skin exfoliation, skin ulceration, sleep disorders, speech disorder, stupor, substernal chest pain, supraventricular tachycardia, syncope, synovitis, tachycardia, tendinitis, thrombocytopenia, tinnitus, tongue edema, tremor, urticaria, ventricular fibrillation, vertigo, weight decrease, WBC abnormal (not otherwise specified), withdrawal syndrome.

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Crystalluria and cylindruria have been reported with other quinolones.

The following laboratory abnormalities appeared in 2.1 to 2.3% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

**Blood Chemistry:** decreased glucose

**Hematology:** decreased lymphocytes

**Post-Marketing Adverse Reactions:**
Additional adverse events reported from worldwide post-marketing experience with levofloxacin include:
- allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, Stevens-Johnson Syndrome, tendon rupture, vasodilation.

**OVERDOSE**

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

**DOSAGE AND ADMINISTRATION**

The usual dose of LEVAQUIN Tablets is 500 mg orally every 24 hours as
described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., $CL_{CR} > 80$ mL/min). For patients with altered renal function (i.e., $CL_{CR} \leq 80$ mL/min), see the Patients with Impaired Renal Function subsection. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multi-vitamin preparations with zinc.

### Patients with Normal Renal Function:

<table>
<thead>
<tr>
<th>Infection*</th>
<th>Unit Dose</th>
<th>Freq.</th>
<th>Duration</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis</td>
<td>500 mg</td>
<td>q24h</td>
<td>7 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Comm. Acquired Pneumonia</td>
<td>500 mg</td>
<td>q24h</td>
<td>7-14 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Acute Maxillary Sinusitis</td>
<td>500 mg</td>
<td>q24h</td>
<td>10-14 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Uncomplicated SSSI</td>
<td>500 mg</td>
<td>q24h</td>
<td>7-10 days</td>
<td>500 mg</td>
</tr>
<tr>
<td>Complicated UTI</td>
<td>250 mg</td>
<td>q24h</td>
<td>10 days</td>
<td>250 mg</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>250 mg</td>
<td>q24h</td>
<td>10 days</td>
<td>250 mg</td>
</tr>
<tr>
<td>Uncomplicated UTI</td>
<td>250 mg</td>
<td>q24h</td>
<td>3 days</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

* DUE TO THE DESIGNATED PATHOGENS (See INDICATIONS AND USAGE.)

### Patients with Impaired Renal Function:

<table>
<thead>
<tr>
<th>Renal Status</th>
<th>Initial Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis / Comm. Acquired Pneumonia / Acute Maxillary Sinusitis / Uncomplicated SSSI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{CR}$ from 50 to 80 mL/min</td>
<td>No dosage adjustment required</td>
<td></td>
</tr>
<tr>
<td>$CL_{CR}$ from 20 to 49 mL/min</td>
<td>500 mg</td>
<td>250 mg q24h</td>
</tr>
<tr>
<td>$CL_{CR}$ from 10 to 19 mL/min</td>
<td>500 mg</td>
<td>250 mg q48h</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>500 mg</td>
<td>250 mg q48h</td>
</tr>
<tr>
<td>CAPD</td>
<td>500 mg</td>
<td>250 mg q48h</td>
</tr>
</tbody>
</table>

### Complicated UTI / Acute Pyelonephritis

<table>
<thead>
<tr>
<th>$CL_{CR}$</th>
<th>Initial Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 20 ) mL/min</td>
<td>No dosage adjustment required</td>
<td></td>
</tr>
<tr>
<td>$CL_{CR}$ from 10 to 19 mL/min</td>
<td>250 mg</td>
<td>250 mg q48h</td>
</tr>
<tr>
<td>Uncomplicated UTI</td>
<td>No dosage adjustment required</td>
<td></td>
</tr>
</tbody>
</table>

$CL_{CR}$=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

**Men:** Creatinine Clearance (mL/min) =

\[
\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}
\]

**Women:** 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.
HOW SUPPLIED

LEV奎因（左氧氟沙星片）片剂被供应为250-和500-mg

modified rectangular, film-coated tablets. LEVAQUIN Tablets are packaged in
bottles and in unit-dose blister strips in the following configurations:

250-mg tablets: color: terra cotta pink
　debossing: "McNeil 1520" on side 1 and "250" on side 2
　bottles of 50 (NDC 0045-1520-50)
　unit-dose/100 tablets (NDC 0045-1520-10)

500-mg tablets: color: peach
　debossing: "McNeil 1525" on side 1 and "500" on side 2
　bottles of 50 (NDC 0045-1525-50)
　unit-dose/100 tablets (NDC 0045-1525-10)

Storage
LEV奎因片剂应存放在15°C至30°C (59°F至85°F) 的密闭容器中。

Also available:

INJECTION
Levofloxacin is also available for intravenous administration in the following
configurations:
LEV奎因注射液（单次使用安瓿）(20 mL) 含有等效于500 mg的左氧氟沙星。

LEV奎因预混液（柔性容器）含有等效于250或500 mg的左氧氟沙星5%的
Dextrose (D₅W).

CLINICAL STUDIES

Community-Acquired Bacterial Pneumonia
Adult inpatients and outpatients with a diagnosis of community-acquired
bacterial pneumonia were evaluated in two pivotal clinical studies. In the first
study, 590 patients were enrolled in a prospective, multi-center, unblinded
randomized trial comparing levofloxacin 500 mg once daily orally or
intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or
in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally
twice daily for a total of 7 to 14 days. Patients assigned to treatment with the
control regimen were allowed to receive erythromycin (or doxycycline if
intolerant of erythromycin) if an infection due to atypical pathogens was
suspected or proven. Clinical and microbiologic evaluations were performed
during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy.
Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days
posttherapy, the primary efficacy variable in this study, was superior (95%) to
the control group (83%) [95% CI of -19.6]. In the second study, 264 patients were enrolled in a prospective, multi-center, noncomparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. Pathogens</th>
<th>Microbiologic Eradication Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>55</td>
<td>98</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>17</td>
<td>88</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>18</td>
<td>94</td>
</tr>
<tr>
<td><em>H. parainfluenzae</em></td>
<td>19</td>
<td>95</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>10</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**ANIMAL PHARMACOLOGY**

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See WARNINGS.) In immature dogs (4 - 5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

*In vitro* and *in vivo* studies in animals indicate that levofloxacin is neither an enzyme inducer or inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
REFERENCES


LEVAQUIN is manufactured and distributed by:

ORTHO PHARMACEUTICAL CORPORATION
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