APPLICATION NUMBER:
21-334 and 21-085/S-010

APPROVED DRAFT LABELING
AVELOX®
(moxifloxacin hydrochloride) Tablets

DESCRIPTION

AVELOX® (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent for oral administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is \( \text{C}_{21}\text{H}_{24}\text{FN}_{3}\text{O}_{4} \cdot \text{HCl} \) and its chemical structure is as follows:

![Chemical Structure of Moxifloxacin]

Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8-position, and an S,S - configured diazabicyclononyl ring moiety at the 7-position.

AVELOX is available in 400 mg (moxifloxacin equivalent) film-coated tablets. The inactive ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and ferric oxide.

CLINICAL PHARMACOLOGY

Absorption

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin.

Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

The mean (± SD) \( C_{\text{max}} \) and AUC values at steady-state with a 400 mg once daily dosage regimen are 4.5 ± 0.53 µg/mL and 48 ± 2.7µg*h/mL, respectively. \( C_{\text{max}} \) is attained 1 to 3 hours after oral dosing. The mean (± SD) trough concentration is 0.95 ± 0.10 µg/mL. Plasma concentrations increase proportionately with dose up
to the highest dose tested (800 mg single dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen. The figure below illustrates the time course of plasma concentrations of moxifloxacin following a 400 mg dose administered at steady-state.

**Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg (mean;SD)**

(n=10)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

**Distribution**

Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral administration of 400 mg. Concentrations measured at 3 hours post-dose are summarized in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.
Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured
3 Hours After Dosing with 400 mg§

<table>
<thead>
<tr>
<th>Tissue or Fluid</th>
<th>N</th>
<th>Plasma Concentration (µg/mL)</th>
<th>Tissue or Fluid Concentration (µg/mL or µg/g)</th>
<th>Tissue: Plasma Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar</td>
<td>5</td>
<td>3.3 ± 0.7</td>
<td>61.8 ± 27.3</td>
<td>21.2 ± 10.0</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial Mucosa</td>
<td>8</td>
<td>3.3 ± 0.7</td>
<td>5.5 ± 1.3</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>Epithelial Lining Fluid</td>
<td>5</td>
<td>3.3 ± 0.7</td>
<td>24.4 ± 14.7</td>
<td>8.7 ± 6.1</td>
</tr>
<tr>
<td>Sinus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary Sinus</td>
<td>4</td>
<td>3.7 ± 1.1†</td>
<td>7.6 ± 1.7</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Mucosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Ethmoid</td>
<td>3</td>
<td>3.7 ± 1.1†</td>
<td>8.8 ± 4.3</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Mucosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Polyps</td>
<td>4</td>
<td>3.7 ± 1.1†</td>
<td>9.8 ± 4.5</td>
<td>2.6 ± 0.6</td>
</tr>
</tbody>
</table>

§ all moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing.
† N = 5

Metabolism
Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Excretion
Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/hr and 2.6 ± 0.5 L/hr, respectively.

Special Populations
Geriatric
In 16 healthy elderly male and female volunteers (66-81 years of age) given a single 200 mg dose of moxifloxacin, the extent of systemic exposure (AUC and Cmax) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age.
Whether pharmacokinetic differences exist between young and elderly females is unknown. The pharmacokinetics of moxifloxacin with repeated 400 mg administration in elderly subjects has not been studied.

**Pediatric**
The pharmacokinetics of moxifloxacin in pediatric subjects have not been studied.

**Gender**
Following a single 200 mg dose of moxifloxacin to 16 healthy elderly subjects, the mean AUC and $C_{\text{max}}$ were 29% and 24% higher, respectively, in healthy elderly females compared to healthy elderly males. There are no significant differences in moxifloxacin pharmacokinetics between elderly male and female subjects when differences in body weight are taken into consideration.

A 400 mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no differences in AUC or Cmax due to gender. Dosage adjustments based on gender are not necessary.

**Race**
Steady state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean $C_{\text{max}}$ of 4.1 µg/mL, an AUC$_{24}$ of 47 µg*h/mL, and an elimination half-life of 14 hours.

**Renal Insufficiency**
The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate, or severe renal impairment. No dosage adjustment is necessary in patients with renal impairment.

In a single-dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations ($C_{\text{max}}$) of moxifloxacin were reduced by 22% and 21% in the patients with moderate (CL$_{\text{CR}}$ ≥ 30 and ≤ 60 mL/min) and severe (CL$_{\text{CR}}$ < 30 mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and Cmax for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively. The sulfate and glucuronide conjugates are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal impairment has not been studied.

The effect of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) on the pharmacokinetics of moxifloxacin has not been studied.
Hepatic Insufficiency

In 400 mg single dose studies in 6 patients with mild (Child Pugh Class A), and 10 patients with moderate (Child Pugh Class B), hepatic insufficiency, moxiﬂoxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls.

The mean AUC of the sulfate conjugate of moxiﬂoxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8.0-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxiﬂoxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6-and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxiﬂoxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See DOSAGE AND ADMINISTRATION.)

Photosensitivity Potential

A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32 healthy volunteers (8 per group) demonstrated that moxiﬂoxacin does not show phototoxicity in comparison to placebo. The minimum erythematosus dose (MED) was measured before and after treatment with moxiﬂoxacin (200 mg or 400 mg once daily), lomeﬂoxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of moxiﬂoxacin were not significantly different from placebo, while lomeﬂoxacin significantly lowered the MED. (See PRECAUTIONS, Information for Patients.)

Drug-drug Interactions

The potential for pharmacokinetic drug interactions between moxiﬂoxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. There was no clinically significant effect of moxiﬂoxacin on theophylline, warfarin, digoxin, or glyburide kinetics. Theophylline, digoxin, probenecid, and ranitidine did not affect the pharmacokinetics of moxiﬂoxacin. However, as with all other quinolones, iron and antacids significantly reduced the bioavailability of moxiﬂoxacin.

Theophylline: No significant effect of moxiﬂoxacin (200 mg every twelve hours for 3 days) on the pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the pharmacokinetics of moxiﬂoxacin. The effect of co-administration of a 400 mg dose of moxiﬂoxacin with theophylline has not been studied, but it is not expected to be clinically significant based on in vitro metabolic data showing that moxiﬂoxacin does not inhibit the CYP1A2 isoenzyme.
**Warfarin:** No significant effect of moxifloxacin (400 mg once daily for eight days) on the pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day) was detected in a study involving 24 healthy volunteers. No significant change in prothrombin time was observed. (See PRECAUTIONS, Drug Interactions.)

**Digoxin:** No significant effect of moxifloxacin (400 mg once daily for two days) on digoxin (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean digoxin $C_{\text{max}}$ increased by about 50% during the distribution phase of digoxin. This transient increase in digoxin $C_{\text{max}}$ is not viewed to be clinically significant. Moxifloxacin pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin or digoxin is required when these drugs are administered concomitantly.

**Probenecid:** Probenecid (500 mg twice daily for two days) did not alter the renal clearance and total amount of moxifloxacin (400 mg single dose) excreted renally in a study of 12 healthy volunteers.

**Ranitidine:** No significant effect of ranitidine (150 mg twice daily for three days as pretreatment) on the pharmacokinetics of moxifloxacin (400 mg single dose) was detected in a study involving 10 healthy volunteers.

**Antidiabetic agents:** In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment and for five days concurrently) mean AUC and $C_{\text{max}}$ were 12% and 21% lower, respectively, when taken with moxifloxacin (400 mg once daily for five days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically significant.

**Antacids:** When moxifloxacin (single 400 mg dose) was administered two hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there was a 26%, 60%, and 23% reduction in the mean AUC of moxifloxacin, respectively. Moxifloxacin should be taken at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See PRECAUTIONS, Drug Interactions and DOSAGE AND ADMINISTRATION.)

**Iron:** When moxifloxacin was administered concomitantly with iron (ferrous sulfate 100 mg once daily for two days), the mean AUC and $C_{\text{max}}$ of moxifloxacin was reduced by 39% and 59%, respectively. Moxifloxacin should only be taken more
than 4 hours before or 8 hours after iron products. (See PRECAUTIONS, Drug
Interactions and DOSAGE AND ADMINISTRATION.)

There is limited information available on the potential for a pharmacodynamic
interaction in humans between moxifloxacin and other drugs that prolong the QTc
interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been
shown to further increase the QTc interval when combined with high doses of
intravenous (IV) moxifloxacin in dogs. Therefore, moxifloxacin should be avoided
with Class IA and Class III antiarrhythmics. (See ANIMAL PHARMACOLOGY,
WARNINGS, and PRECAUTIONS.)

MICROBIOLOGY
Moxifloxacin has in vitro activity against a wide range of Gram-positive and Gram-
negative microorganisms. The bactericidal action of moxifloxacin results from
inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for
bacterial DNA replication, transcription, repair, and recombination. It appears
that the C8-methoxy moiety contributes to enhanced activity and lower selection of
resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

The mechanism of action for quinolones, including moxifloxacin, is different from
that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore,
microorganisms resistant to these classes of drugs may be susceptible to
moxifloxacin and other quinolones. There is no known cross-resistance between
moxifloxacin and other classes of antimicrobials.

Cross-resistance has been observed between moxifloxacin and other
fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria
resistant to other fluoroquinolones may, however, still be susceptible to
moxifloxacin.

Moxifloxacin 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
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following in vitro data are available, but their clinical significance is unknown.

Moxifloxacin exhibits in vitro minimum inhibitory concentrations (MICs) of 2 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
Streptococcus viridans group

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Legionella pneumophila
Proteus mirabilis

Anaerobic microorganisms
Fusobacterium species
Peptostreptococcus species
Prevotella species

Susceptibility Tests
Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum 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 method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:
For testing Enterobacteriaceae and Staphylococcus species:

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>4.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing Haemophilus influenzae and Haemophilus parainfluenzae a:

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

a This interpretive standard is applicable only to broth microdilution susceptibility tests with Haemophilus influenzae and Haemophilus parainfluenzae using Haemophilus Test Medium.

The current absence of data on resistant strains precludes defining any results 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 species including Streptococcus pneumoniae b:

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2.0</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

b This interpretive standard is 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 moxifloxacin powder should provide 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>0.06 - 0.5</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25922</td>
<td>0.008 - 0.06</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>ATCC 49247&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.008 - 0.03</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>29213</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>ATCC 49619&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.06 - 0.25</td>
</tr>
</tbody>
</table>

<sup>c</sup> This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)<sup>1</sup>.

<sup>d</sup> 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<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg moxifloxacin to test the susceptibility of microorganisms to moxifloxacin.

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

The following zone diameter interpretive criteria should be used for testing Enterobacteriaceae and *Staphylococcus* species:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 19</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16 - 18</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>6</sup>:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 18</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>
This zone diameter standard is applicable only to tests with Haemophilus influenzae and Haemophilus parainfluenzae using Haemophilus Test Medium (HTM)

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

For testing Streptococcus species including Streptococcus pneumoniae:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 18</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>15 - 17</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 14</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

These interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton agar supplemented with 5% sheep blood 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 moxifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg moxifloxacin 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>Haemophilus influenzae</em></td>
<td>ATCC 49274</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>ATCC 25923</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>ATCC 49619</td>
</tr>
</tbody>
</table>

These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)

These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

INDICATIONS AND USAGE

AVELOX Tablets are indicated for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the
conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

**Acute Bacterial Sinusitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*.

**Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus*, or *Moraxella catarrhalis*.

**Community Acquired Pneumonia** (of mild to moderate severity) caused by *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae*, or *Moraxella catarrhalis*.

**Uncomplicated Skin and Skin Structure Infections** caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.

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

**CONTRAINDICATIONS**

Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

**WARNINGS**

**THE SAFETY AND EFFECTIVENESS OF MOXIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PRECAUTIONS-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS SUBSECTIONS.)**

**MOXIFLOXACIN HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. THE DRUG SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTARRHYTHMIC AGENTS, DUE TO THE LACK OF CLINICAL EXPERIENCE WITH THE DRUG IN THESE PATIENT POPULATIONS.**
Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore moxifloxacin should be used with caution when given concurrently with these drugs.

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied, however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

The magnitude of QT prolongation may increase with increasing concentrations of the drug, therefore the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. In 787 patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 4000 patients in controlled clinical studies, and there was no increase in mortality in over 18,000 patients in a post-marketing observational study. However certain predisposing conditions may increase the risk for ventricular arrhythmias.

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See PRECAUTIONS: General, Information for Patients, and ADVERSE REACTIONS.)

Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including moxifloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin
should be discontinued at the first appearance of a skin rash or any other sign of
hypersensitivity. Oxygen, intravenous steroids, and airway management, including
intubation, may be administered as indicated.

Severe and sometimes fatal events, some due to hypersensitivity, and some of
uncertain etiology, have been reported in patients receiving therapy with all
antibiotics. These events may be severe and generally occur following the
administration of multiple doses. Clinical manifestations may include one or more
of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

Pseudomembranous colitis has been reported with nearly all antibacterial
agents 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 antibacterial agents.

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.

Although not observed in moxifloxacin clinical trials, Achilles and other tendon
ruptures that required surgical repair or resulted in prolonged disability have been
reported with quinolones. Moxifloxacin should be discontinued if the patient
experiences pain, inflammation, or rupture of a tendon.

PRECAUTIONS

General: Quinolones may cause central nervous system (CNS) events, including:
nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See
WARNINGS and Information for Patients.)

Information for Patients:
To assure safe and effective use of moxifloxacin, the following information and
instructions should be communicated to the patient when appropriate:

Patients should be advised:

that moxifloxacin may produce changes in the electrocardiogram (QTc interval
prolongation).
that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.

that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.

to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.

to inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.

to contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.

that moxifloxacin may be taken with or without meals, and to drink fluids liberally.

that moxifloxacin should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminum), sucralfate, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See CLINICAL PHARMACOLOGY, Drug Interactions and PRECAUTIONS, Drug Interactions.)

that moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.

to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

that moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with moxifloxacin at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If sunburn-like reaction or skin eruptions occur, contact your physician. (See CLINICAL PHARMACOLOGY, Photosensitivity Potential.)
that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.
Drug Interactions:
Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing aluminum, magnesium, or calcium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before or 8 hours after these agents. (See CLINICAL PHARMACOLOGY, Drug Interactions and DOSAGE AND ADMINISTRATION.)

No clinically significant drug-drug interactions between theophylline, warfarin, digoxin, or glyburide have been observed with moxifloxacin. Theophylline, digoxin, probenecid, and ranitidine have been shown not to alter the pharmacokinetics of moxifloxacin. (See CLINICAL PHARMACOLOGY.)

Warfarin: No significant effect of moxifloxacin on R- and S- warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin. However, since some quinolones have been reported to enhance the anticoagulant effects of 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.

Drugs metabolized by Cytochrome P450 enzymes: in vitro studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (e.g. midazolam, cyclosporine, warfarin, theophylline).

Nonsteroidal anti-inflammatory drugs (NSAIDs): Although not observed with moxifloxacin in preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions. (See WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was
clastogenic in the v79 chromosome aberration assay, but it did not induce
unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of
genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high
as 500 mg/kg/day, approximately 12 times the maximum recommended human
dose based on body surface area (mg/m²). At 500 mg/kg there were slight
effects on sperm morphology (head-tail separation) in male rats and on the
estrous cycle in female rats.

Pregnancy: Teratogenic Effects. Pregnancy Category C:
Moxifloxacin was not teratogenic when administered to pregnant rats during
organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the
maximum recommended human dose based on systemic exposure (AUC), but
decreased fetal body weights and slightly delayed fetal skeletal development
(indicative of fetotoxicity) were observed. Intravenous administration of 20
mg/kg/day (approximately equal to the maximum recommended human oral dose
based upon systemic exposure) to pregnant rabbits during organogenesis resulted
in decreased fetal body weights and delayed fetal skeletal ossification. When rib
and vertebral malformations were combined, there was an increased fetal and
litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose
included mortality, abortions, marked reduction of food consumption, decreased
water intake, body weight loss and hypoactivity. There was no evidence of
teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high
as 100 mg/kg/day (2.5 times the maximum recommended human dose based
upon systemic exposure). An increased incidence of smaller fetuses was
observed at 100 mg/kg/day. In an oral pre- and postnatal development study
conducted in rats, effects observed at 500 mg/kg/day included slight increases in
duration of pregnancy and prenatal loss, reduced pup birth weight and decreased
neonatal survival. Treatment-related maternal mortality occurred during gestation
at 500 mg/kg/day in this study.

Since there are no adequate or well-controlled studies in pregnant women,
moxifloxacin should be used during pregnancy only if the potential benefit justifies
the potential risk to the fetus.

Nursing Mothers: Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin
may also be excreted in human milk. Because of the potential for serious adverse
reactions in infants nursing from mothers taking moxifloxacin, 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 pediatric patients and adolescents less
than 18 years of age have not been established. Moxifloxacin causes arthropathy
in juvenile animals. (See WARNINGS.)
Geriatric Use: In controlled multiple-dose clinical trials, 23% of patients receiving moxifloxacin were greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of moxifloxacin in patients aged 65 or older compared to younger adults.

ADVERSE REACTIONS

Clinical efficacy trials enrolled over 4900 moxifloxacin treated patients, of whom over 4300 patients received the 400 mg dose. Most adverse events reported in moxifloxacin trials were described as mild to moderate in severity and required no treatment. Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 3.8% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of moxifloxacin treated patients were:
- Nausea (8%), diarrhea (6%), dizziness (3%), headache (2%), abdominal pain (2%), vomiting (2%), taste perversion (1%), abnormal liver function test (1%), and dyspepsia (1%).

Additional events, judged by investigators to be at least possibly drug-related, that occurred in greater than 0.05% and less than 1% of moxifloxacin treated patients were:

BODY AS A WHOLE: asthenia, moniliasis, pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain, pelvic pain, abdominal pain, back pain, chills, infection, chest pain, hand pain
CARDIOVASCULAR: palpitation, vasodilatation, tachycardia, hypertension, peripheral edema, hypotension
CENTRAL NERVOUS SYSTEM: insomnia, nervousness, anxiety, confusion, hallucinations, depersonalization, hypertonia, incoordination, somnolence, tremor, vertigo, paresthesia
DIGESTIVE: dry mouth, constipation, oral moniliasis, anorexia, stomatitis, gastritis, glossitis, gastrointestinal disorder, cholestatic jaundice, GGTP increased
HEMATIC AND LYMPHATIC: prothrombin time decrease, prothrombin time increase, thrombocytopenia, thrombocytopenia, eosinophilia, leukopenia
METABOLIC AND NUTRITIONAL: amylase increased, hyperglycemia, hyperlipidemia, lactic dehydrogenase increased
MUSCULOSKELETAL: arthralgia, myalgia
RESPIRATORY: asthma, dyspnea, cough increased, pneumonia, pharyngitis, rhinitis, sinusitis
SKIN/APPENDAGES: rash, pruritus, sweating, urticaria, dry skin
SPECIAL SENSES: tinnitus, amblyopia
UROGENITAL: vaginal moniliasis, vaginitis, cystitis, kidney function abnormal
Post-Marketing Adverse Event Reports:
Additional adverse events reported from worldwide post-marketing experience with moxifloxacin include anaphylactic reaction and anaphylactic shock.

LABORATORY CHANGES
Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in ≥ 2% of patients and at an incidence greater than in controls included: increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin, bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose, 2PO2, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSAGE
In the event of acute overdosage, the stomach should be emptied and ECG monitoring is recommended due to the possible prolongation of the QT interval. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. It is not known whether moxifloxacin is dialyzable.

Single oral moxifloxacin doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was 100 mg/kg. Toxic signs after administration of a single high dose of moxifloxacin to these animals included CNS and gastrointestinal effects such as decreased activity, somnolence, tremor, convulsions, vomiting and diarrhea.

DOSAGE AND ADMINISTRATION
The dose of AVELOX Tablets is one 400 mg tablet taken orally every 24 hours. The duration of therapy depends on the type of infection as described below.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Daily Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bacterial Sinusitis</td>
<td>400 mg</td>
<td>10 days</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis</td>
<td>400 mg</td>
<td>5 days</td>
</tr>
<tr>
<td>Community Acquired Pneumonia</td>
<td>400 mg</td>
<td>10 days</td>
</tr>
<tr>
<td>Uncomplicated Skin and Skin Structure Infections</td>
<td>400 mg</td>
<td>7 days</td>
</tr>
</tbody>
</table>

* due to the designated pathogens (See INDICATIONS AND USAGE.)
Oral doses of moxifloxacin should be administered at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution.

(See CLINICAL PHARMACOLOGY, Drug Interactions and PRECAUTIONS, Drug Interactions.)

Impaired Renal Function
No dosage adjustment is required in renally impaired patients. Moxifloxacin has not been studied in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired Hepatic Function
No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See CLINICAL PHARMACOLOGY, Hepatic Insufficiency.)

HOW SUPPLIED
AVELOX (moxifloxacin hydrochloride) Tablets are available as oblong, dull red film-coated tablets containing 400 mg moxifloxacin. The tablet is coded with the word "BAYER" on one side and "M400" on the reverse side.

<table>
<thead>
<tr>
<th>Package</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottles of 30:</td>
<td>0026-8581-69</td>
</tr>
<tr>
<td>ABC Pack of 5:</td>
<td>0026-8581-41</td>
</tr>
</tbody>
</table>

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Avoid high humidity.

ANIMAL PHARMACOLOGY
Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin ≥ 30 mg/kg/day (approximately 1.5 times the maximum recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy. There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and 500 mg/kg, respectively.

Unlike some other members of the quinolone class, crystalluria was not observed in 6 month repeat dose studies in rats and monkeys with moxifloxacin.

Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys. In beagle dogs, electroretinographic (ERG) changes were observed in a 2 week study at doses of 60 and 90 mg/kg. Histopathological changes were observed in the retina from one of four dogs at 90 mg/kg, a dose associated with mortality in this study.
Some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDS). Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (e.g. seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.

In animal studies, at plasma concentrations about five times the human therapeutic level, a QT-prolonging effect of moxifloxacin was found. Electrophysiological in vitro studies suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism. In dogs, the combined infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the same dose (30mg/kg) of moxifloxacin alone.

**CLINICAL STUDIES**

**Acute Bacterial Exacerbation of Chronic Bronchitis**

AVELOX Tablets (400 mg once daily for five days) were evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in a large, randomized, double-blind, controlled clinical trial conducted in the US. This study compared AVELOX with clarithromycin (500 mg twice daily for 10 days) and enrolled 629 patients. The primary endpoint for this trial was clinical success at 7-17 days post-therapy. The clinical success for AVELOX was 89% (222/250) compared to 89% (224/251) for clarithromycin.

The following outcomes are the clinical success rates at the follow-up visit for the clinically evaluable patient groups by pathogen:

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>AVELOX</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>100% (16/16)</td>
<td>87% (20/23)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>89% (33/37)</td>
<td>88% (36/41)</td>
</tr>
<tr>
<td><em>Haemophilus parainfluenzae</em></td>
<td>100% (16/16)</td>
<td>100% (14/14)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>85% (29/34)</td>
<td>100% (24/24)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>94% (15/16)</td>
<td>75% (6/8)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>90% (18/20)</td>
<td>91% (10/11)</td>
</tr>
</tbody>
</table>

The microbiological eradication rates (eradication plus presumed eradication) in AVELOX treated patients were *Streptococcus pneumoniae* 100%, *Haemophilus influenzae* 89%, *Haemophilus parainfluenzae* 100%, *Moraxella catarrhalis* 85%, *Staphylococcus aureus* 94%, and *Klebsiella pneumoniae* 85%.

**Community Acquired Pneumonia**

A large, randomized, double-blind, controlled clinical trial was conducted in the US to compare the efficacy of AVELOX Tablets (400 mg once daily) to that of high-dose clarithromycin (500 mg twice daily) in the treatment of patients with clinically
and radiologically documented community acquired pneumonia. This study enrolled
474 patients (382 of which were valid for the primary efficacy analysis conducted
at the 14 - 35 day follow-up visit). Clinical success for clinically evaluable patients
was 95% (184/194) for AVELOX and 95% (178/188) for high dose clarithromycin.

In addition to the trial described above, a noncomparative trial of AVELOX (400
mg once daily for ten days) was also conducted in the US in patients with
community acquired pneumonia. The combined moxifloxacin clinical success rates
by pathogen for the two studies were as follows:

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>14 - 35 DAY FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>97% (30/31)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>92% (33/36)</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>96% (51/53)</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>93% (106/114)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>91% (10/11)</td>
</tr>
</tbody>
</table>

The microbiological eradication rates (eradication plus presumed eradication) in
AVELOX treated patients were *Streptococcus pneumoniae* 97%, *Haemophilus
influenzae* 92%, and *Moraxella catarrhalis* 91%.

**Acute Bacterial Sinusitis**

In a large, controlled double-blind study conducted in the US, AVELOX (400 mg
once daily for ten days) was compared with cefuroxime axetil (250 mg twice daily
for ten days) for the treatment of acute bacterial sinusitis. The trial included 457
patients valid for the primary efficacy determination. Clinical success (cure plus
improvement) at the 7 to 21 day post-therapy test of cure visit was 90% for
AVELOX and 89% for cefuroxime.

An additional non-comparative study was conducted to gather bacteriological data
and to evaluate microbiological eradication in adult patients treated with AVELOX
400 mg once daily for seven days. All patients (n = 336) underwent antral
puncture in this study. Clinical success rates and eradication/presumed
eradication rates at the 21 to 37 day follow-up visit were 97% (29 out of 30) for
*Streptococcus pneumoniae*, 83% (15 out of 18) for *Moraxella catarrhalis*, and
80% (24 out of 30) for *Haemophilus influenzae*. 
Uncomplicated Skin and Skin Structure Infections

A randomized, double-blind, controlled clinical trial conducted in the US compared the efficacy of AVELOX 400 mg once daily for seven days with Cephalexin HCl 500 mg three times daily for seven days. The percentage of patients treated for uncomplicated abscesses was 30%, furuncles 8%, cellulitis 16%, impetigo 20%, and other skin infections 26%. Adjunctive procedures (incision and drainage or debridement) were performed on 17% of the AVELOX treated patients and 14% of the comparator treated patients. Clinical success rates in evaluable patients were 89% (108/122) for AVELOX and 91% (110/121) for Cephalexin HCl.

REFERENCES

Patient Information About:

AVELOX®
(moxifloxacin hydrochloride)
400 mg Tablets

This section contains important information about AVELOX (moxifloxacin hydrochloride), and should be read completely before you begin treatment. This section does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of AVELOX. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about AVELOX talk with your health care professional. Only your health care professional can determine if AVELOX is right for you.

What is AVELOX?

AVELOX is an antibiotic used to treat lung, sinus, or skin infections caused by certain germs called bacteria. AVELOX kills many of the types of bacteria that can infect the lungs and sinuses and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). AVELOX, like all other antibiotics, does not kill viruses.
You should contact your doctor if you think your condition is not improving while taking AVELOX. AVELOX Tablets are red and contain 400 mg of active drug.

**How and when should I take AVELOX?**

AVELOX should be taken once a day for 5, 7, or 10 days depending on your prescription. It should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of AVELOX even if you missed a dose by mistake. You should not take a double dose.

**Who should not take AVELOX?**

You should not take AVELOX if you have ever had a severe allergic reaction to any of the group of antibiotics known as “quinolones” such as ciprofloxacin or levofloxacin.

You should avoid AVELOX if you have a rare condition known as congenital prolongation of the QT interval. If you or any of your family members have this condition you should inform your health care professional. You should avoid AVELOX if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone or sotalol. Inform your health care professional if you are taking a heart rhythm drug.

You should also avoid AVELOX if the amount of potassium in your blood is low. Low potassium can sometimes be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic medicine you should speak with your health care professional.

If you are pregnant or planning to become pregnant while taking AVELOX, talk to your doctor before taking this medication. AVELOX is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

AVELOX is not recommended for children.

**What are the possible side effects of AVELOX?**

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include nausea, vomiting, stomach pain, diarrhea, dizziness and headache. You should be careful about driving or operating machinery until you are sure AVELOX is not causing dizziness. If you notice any side effects not mentioned in this section or you have any concerns
about the side effects you are experiencing, please inform your health care professional.

In some people, AVELOX, as with some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any serious problems in more than 4000 patients who have already taken the medication in clinical studies, in theory it could result in extremely rare cases of abnormal heartbeat which may be dangerous. Contact your health care professional if you develop heart palpitations (fast beating), or have fainting spells.

**Which medicines should not be used with AVELOX?**

You should avoid taking AVELOX with certain medicines used to treat an abnormal heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

Some medicines also produce an effect on the electrocardiogram test, including cisapride, erythromycin, some antidepressants and some antipsychotic drugs. These may increase the risk of heartbeat problems when taken with AVELOX. For this reason it is important to let your health care provider know all of the medicines that you are using.

Many antacids and multivitamins may interfere with the absorption of AVELOX and may prevent it from working properly. You should take AVELOX either 4 hours before or 8 hours after taking these products.

**Remember**

Take your dose of AVELOX once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

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