

Active Ingredient Search Results from "Rx" table for query on "levofloxacin."

| Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant |
|---------|---------|-----|-------------------|----------------------------|-------------|--|--------------------|
| 020635 | | Yes | LEVOFLOXACIN | Injectable; Injection | 25MG/ML | LEVAQUIN | ORTHO MCNEIL PHARM |
| 020635 | | Yes | LEVOFLOXACIN | Injectable; Injection | 500MG/100ML | LEVAQUIN IN DEXTROSE 5% IN PLASTIC CONTAINER | ORTHO MCNEIL PHARM |
| 020635 | | Yes | LEVOFLOXACIN | Injectable; Injection | 5MG/ML | LEVAQUIN IN DEXTROSE 5% IN PLASTIC CONTAINER | ORTHO MCNEIL PHARM |
| 021199 | | Yes | LEVOFLOXACIN | Solution/Drops; Ophthalmic | 0.5% | QUIXIN | SANTEN |
| 020634 | | No | LEVOFLOXACIN | Tablet; Oral | 250MG | LEVAQUIN | ORTHO MCNEIL PHARM |
| 020634 | | No | LEVOFLOXACIN | Tablet; Oral | 500MG | LEVAQUIN | ORTHO MCNEIL PHARM |
| 020634 | | Yes | LEVOFLOXACIN | Tablet; Oral | 750MG | LEVAQUIN | ORTHO MCNEIL PHARM |

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Active Ingredient Search Results from "Rx" table for query on "trovafloxacin."

| Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant |
|---------|---------|-----|------------------------|--------------------|---------------|------------------|-----------|
| 020759 | | No | TROVAFLOXACIN MESYLATE | Tablet; Oral | EQ 100MG BASE | TROVAN | PFIZER |
| 020759 | | Yes | TROVAFLOXACIN MESYLATE | Tablet; Oral | EQ 200MG BASE | TROVAN | PFIZER |

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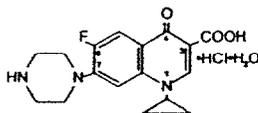
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CIPRO®
(ciprofloxacin hydrochloride)
TABLETS
CIPRO®
(ciprofloxacin*)
ORAL SUSPENSION

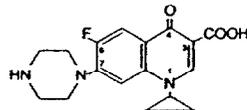
08858082

DESCRIPTION

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolonecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{19}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:



Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolonecarboxylic acid. Its empirical formula is $C_{17}H_{19}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



CIPRO film-coated tablets are available in 100 mg, 250 mg, 500 mg and 750 mg (ciprofloxacin equivalent) strengths. Ciprofloxacin tablets are white to slightly yellowish. The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, croscopolone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and water.

Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions for USE/HANDLING). The components of the suspension have the following compositions: Microcapsules - ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and Polysorbate 20.

Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.
* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

CLINICAL PHARMACOLOGY

Absorption: Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations and area under the curve are shown in the chart for the 250 mg to 1000 mg dose range.

| Dose (mg) | Maximum Serum Concentration ($\mu\text{g/mL}$) | Area Under Curve (AUC) ($\mu\text{g}\cdot\text{hr/mL}$) |
|-----------|--|---|
| 250 | 1.2 | 4.8 |
| 500 | 2.4 | 11.6 |
| 750 | 4.3 | 20.2 |
| 1000 | 5.4 | 30.8 |

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 $\mu\text{g/mL}$, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a C_{max} similar to that observed with a 400 mg I.V. dose. A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

Steady-state Pharmacokinetic Parameters Following Multiple Oral and I.V. Doses

| Parameters | 500 mg q12h, P.O. | 400 mg q12h, I.V. | 750 mg q12h, P.O. | 400 mg q8h, I.V. |
|---|----------------------|----------------------|----------------------|---------------------|
| AUC ($\mu\text{g}\cdot\text{hr/mL}$) | 13.7 ^a | 12.7 ^a | 31.6 ^b | 32.9 ^c |
| C_{max} ($\mu\text{g/mL}$) | 2.97 | 4.56 | 3.59 | 4.07 |
| ^a AUC _{0-12h}} | | | | |
| ^b AUC 24h=AUC _{0-12h} x 2 | | | | |
| ^c AUC 24h=AUC _{0-8h} x 3 | | | | |

Distribution: The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism: Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Excretion: The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 $\mu\text{g/mL}$ during the first two hours and are approximately 30 $\mu\text{g/mL}$ at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

With oral administration, a 500 mg dose, given as 10 mL of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to the 500 mg tablet. A 10 mL volume of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO Suspension (containing 500 mg ciprofloxacin/5mL).

Drug-Drug Interactions: When CIPRO Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when CIPRO Suspension is given with food. The overall absorption of CIPRO Tablet or CIPRO Suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See PRECAUTIONS.)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See PRECAUTIONS.)
Special Populations: Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS: Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

In primary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vivo* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin 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 of the package insert for CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms

- Enterococcus faecalis* (Many strains are only moderately susceptible.)
- Staphylococcus aureus* (methicillin-susceptible strains only)
- Staphylococcus epidermidis* (methicillin-susceptible strains only)
- Staphylococcus saprophyticus*
- Streptococcus pneumoniae* (penicillin-susceptible strains only)
- Streptococcus pyogenes*

Aerobic gram-negative microorganisms

- Campylobacter jejuni*
- Citrobacter diversus*
- Citrobacter freundii*
- Enterobacter cloacae*
- Escherichia coli*
- Haemophilus influenzae*
- Haemophilus parainfluenzae*
- Klebsiella pneumoniae*
- Moraxella catarrhalis*
- Morganella morganii*
- Nisseria gonorrhoeae*
- Proteus mirabilis*
- Proteus vulgaris*
- Providencia rettgeri*
- Providencia stuartii*
- Pseudomonas aeruginosa*
- Salmonella typhi*
- Serratia marcescens*
- Shigella boydii*
- Shigella dysenteriae*
- Shigella flexneri*
- Shigella sonnei*

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see INDICATIONS AND USAGE and INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION).

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

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 $\mu\text{g/mL}$ or less against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

- Staphylococcus haemolyticus*
- Staphylococcus hominis*
- Streptococcus pneumoniae* (penicillin-resistant strains only)

Aerobic gram-negative microorganisms

- Acinetobacter lwoffii*
- Aeromonas hydrophila*
- Edwardsiella ictalura*
- Enterobacter aerogenes*
- Klebsiella oxytoca*
- Legionella pneumophila*
- Pasteurella multocida*
- Salmonella enteritidis*
- Vibrio cholerae*
- Vibrio parahaemolyticus*
- Vibrio vulnificus*
- Yersinia enterocolitica*

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

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 ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Nisseria gonorrhoeae*:

| MIC ($\mu\text{g/mL}$) | Interpretation |
|--------------------------|------------------|
| ≤ 1 | Susceptible (S) |
| 2 | Intermediate (I) |
| ≥ 4 | Resistant (R) |

¹These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:

| MIC ($\mu\text{g/mL}$) | Interpretation |
|--------------------------|-----------------|
| ≤ 1 | Susceptible (S) |

²This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium¹.

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

For testing *Nisseria gonorrhoeae*:

| MIC ($\mu\text{g/mL}$) | Interpretation |
|--------------------------|------------------|
| ≤ 0.06 | Susceptible (S) |
| 0.12 - 0.5 | Intermediate (I) |
| ≥ 1 | Resistant (R) |

³This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

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 high dosage of drug can be used. This category also provides a buffer zone, which prevents small or 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 ciprofloxacin powder should provide the following MIC values:

| Organism | ATCC | MIC ($\mu\text{g/mL}$) |
|------------------------------------|------------|--------------------------|
| <i>E. faecalis</i> | ATCC 29212 | 0.25 - 2.0 |
| <i>E. coli</i> | ATCC 25922 | 0.004 - 0.015 |
| <i>H. influenzae</i> ^a | ATCC 49247 | 0.004 - 0.03 |
| <i>N. gonorrhoeae</i> ^b | ATCC 49226 | 0.001 - 0.008 |
| <i>P. aeruginosa</i> | ATCC 27853 | 0.25 - 1.0 |
| <i>S. aureus</i> | ATCC 29213 | 0.12 - 0.5 |

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

^bThis quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

Dilution Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5- μg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*:

| Zone Diameter (mm) | Interpretation |
|--------------------|------------------|
| ≥ 21 | Susceptible (S) |
| 16 - 20 | Intermediate (I) |
| ≤ 15 | Resistant (R) |

* These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:

| Zone Diameter (mm) | Interpretation |
|--------------------|-----------------|
| ≥ 21 | Susceptible (S) |

* This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium (HTM)².

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 *Neisseria gonorrhoeae*:

| Zone Diameter (mm) | Interpretation |
|--------------------|------------------|
| ≥ 41 | Susceptible (S) |
| 28 - 40 | Intermediate (I) |
| ≤ 27 | Resistant (R) |

* This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement. 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 ciprofloxacin.

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 ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

| Organism | ATCC | Zone Diameter (mm) |
|------------------------------------|------------|--------------------|
| <i>E. coli</i> | ATCC 25922 | 30 - 40 |
| <i>H. influenzae</i> ^a | ATCC 49247 | 34 - 42 |
| <i>N. gonorrhoeae</i> ^b | ATCC 49226 | 48 - 58 |
| <i>P. aeruginosa</i> | ATCC 27853 | 25 - 33 |
| <i>S. aureus</i> | ATCC 25923 | 22 - 30 |

* These quality control limits are applicable only to *H. influenzae* ATCC 49247 testing using Haemophilus Test Medium (HTM)².

^b These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

INDICATIONS AND USAGE

CIPRO is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*. (See DOSAGE AND ADMINISTRATION.)

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

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

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*.

Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*. (See DOSAGE AND ADMINISTRATION.)

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii*¹, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei*¹ when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*.

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae*.

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.⁴ (See also, **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**.)

¹ Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered. 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 ciprofloxacin. Therapy with CIPRO may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE) - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.) The oral administration of ciprofloxacin caused lameness in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin 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 ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders 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 FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, leukocytosis, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomonas aeruginosa has been reported with nearly all antibiograms, including ciprofloxacin, 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 antibiograms.

Treatment with antibiogram 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 pseudomonas colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomonas 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 antibiogram drug clinically effective against *C. difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Post-marketing surveillance reports indicate that the risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See ANIMAL PHARMACOLOGY.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

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

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients:

Patients should be advised:

- that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Veder® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these products.

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

- to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.

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

- that ciprofloxacin 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 ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.

- that convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See WARNINGS.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, Veder® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired. (See DOSAGE AND ADMINISTRATION for concurrent administration of these agents with ciprofloxacin.)

Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin. The concomitant administration of ciprofloxacin with the sulfonurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Animal studies have shown that the combination of very high doses of quinolones and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Macronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m²), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.¹

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by IERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data-fair), but the data are insufficient to state that there is no risk.²

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.³ In utero exposure to fluoroquinolones during

embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 495 pregnancies with fluoroquinolone exposure (93% first trimester exposures). There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.¹⁸ However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see WARNINGS).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See WARNINGS.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, 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, except for use in inhalational anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (post-exposure), see DOSAGE AND ADMINISTRATION and INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION.

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin 1.0, 1.0 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime 1.0, 50 mg/kg/dose q8h and tobramycin 1.0, 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin cannot be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

Geriatric Use: In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.0% of orally treated patients. The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

Additional medically important events that occurred in less than 1% of ciprofloxacin patients are listed below.

- BODY AS A WHOLE:** headache, abdominal pain/discomfort, foot pain, pain in extremities, injection site reaction (ciprofloxacin intravenous)
- CARDIOVASCULAR:** palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypertension
- CENTRAL NERVOUS SYSTEM:** restlessness, dizziness, light-headedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, abnormal gait, grand mal convulsion
- GASTROINTESTINAL:** painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, hepatitis
- HEMICALYMPHATIC:** lymphadenopathy, petechia
- METABOLIC/NUTRITIONAL:** amylase increase, lipase increase
- MUSCULOSKELETAL:** arthralgia or back pain, joint stiffness, actinemia, neck or chest pain, flare up of gout
- RENAL/UROGENITAL:** interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, xerosis, breast pain
- RESPIRATORY:** dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism
- SKIN/HYPERSENSITIVITY:** pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctiva or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating
- SPECIAL SENSES:** blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg BID) to cefuroxime axetil (250 mg q 12h) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Post-Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hypersensitivity, hyperkalemia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, mononucleosis (oral, gastrointestinal, vaginal), myasthenia, myasthenia gravis (possible exacerbation), myoclonus, myasthenus, pancreatitis, pancytopenia (life threatening or fatal outcome), phenylalanine alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic, renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See PRECAUTIONS.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below.

- Hepatic** - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).
- Hematologic** - Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).
- Renal** - Elevations of serum creatinine (1.1%), BUN (0.9%), CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

OVERDOSAGE

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function and administration of magnesium or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post-treatment observation period at the highest oral doses tested, up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypocoxy and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

DOSAGE AND ADMINISTRATION

CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Vide® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.

DOSAGE GUIDELINES

| Infection | Type or Severity | Unit Dose | Frequency | Usual Duration* |
|---|--|--|-------------|-----------------|
| Urinary Tract | Acute/Uncomplicated | 100 mg or 250 mg | q 12 h | 3 Days |
| | Mild/Moderate | 250 mg | q 12 h | 7 to 14 Days |
| | Severe/Complicated | 500 mg | q 12 h | 7 to 14 Days |
| Chronic Bacterial Prostatitis | Mild/Moderate | 500 mg | q 12 h | 28 Days |
| Lower Respiratory Tract | Mild/Moderate | 500 mg | q 12 h | 7 to 14 days |
| | Severe/Complicated | 750 mg | q 12 h | 7 to 14 days |
| Acute Sinusitis | Mild/Moderate | 500 mg | q 12 h | 10 days |
| Skin and Skin Structure | Mild/Moderate | 500 mg | q 12 h | 7 to 14 Days |
| | Severe/Complicated | 750 mg | q 12 h | 7 to 14 Days |
| Bone and Joint | Mild/Moderate | 500 mg | q 12 h | ≥ 4 to 6 weeks |
| | Severe/Complicated | 750 mg | q 12 h | ≥ 4 to 6 weeks |
| Intra-Abdominal† | Complicated | 500 mg | q 12 h | 7 to 14 Days |
| Infectious Diarrhea | Mild/Moderate/Severe | 500 mg | q 12 h | 5 to 7 Days |
| Typhoid Fever | Mild/Moderate | 500 mg | q 12 h | 10 Days |
| Urethral and Cervical Gonococcal Infections | Uncomplicated | 250 mg | single dose | single dose |
| | Inhalational anthrax (post-exposure)** | Adult 500 mg Pediatric 15 mg/kg per dose, not to exceed 500 mg per dose | q 12 h | 60 Days |

* used in conjunction with metronidazole

† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).

** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.* For a discussion of ciprofloxacin serum concentrations in various human populations, see INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION.

Patients whose therapy is started with CIPRO I.V. may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of the physician (See CLINICAL PHARMACOLOGY and table below for the equivalent dosing regimens).

Equivalent AUC Dosing Regimens

| Given Oral Dosage | Equivalent Given I.V. Dosage |
|----------------------|------------------------------|
| 250 mg Tablet q 12 h | 200 mg I.V. q 12 h |
| 500 mg Tablet q 12 h | 400 mg I.V. q 12 h |
| 750 mg Tablet q 12 h | 400 mg I.V. q 8 h |

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

| Creatinine Clearance (mL/min) | Dose |
|---|--------------------------------------|
| > 50 | See Usual Dosage. |
| 30 - 50 | 250 - 500 mg q 12 h |
| 5 - 29 | 250 - 500 mg q 18 h |
| Patients on hemodialysis or Peritoneal dialysis | 250 - 500 mg q 24 h (after dialysis) |

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

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

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

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1 - 2 hours after dosing) should generally range from 2 to 4 µg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

HOW SUPPLIED

CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 100 mg or 250 mg ciprofloxacin. The 100 mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side. The 250 mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO is also available as capsule shaped, slightly yellowish film-coated tablets containing 500 mg or 750 mg ciprofloxacin. The 500 mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750 mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO 250 mg, 500 mg, and 750 mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100 mg strength is available only as CIPRO Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.

| | Strength | NDC Code | Tablet Identification |
|---------------------------|----------|------------------|-----------------------|
| Bottles of 50: | 750 mg | NDC 0026-8514-50 | CIPRO 750 |
| Bottles of 100: | 250 mg | NDC 0026-8512-51 | CIPRO 250 |
| | 500 mg | NDC 0026-8513-51 | CIPRO 500 |
| Unit Dose Package of 100: | 250 mg | NDC 0026-8512-48 | CIPRO 250 |
| | 500 mg | NDC 0026-8513-48 | CIPRO 500 |
| | 750 mg | NDC 0026-8514-48 | CIPRO 750 |
| Cystitis Package of 6: | 100 mg | NDC 0026-8511-06 | CIPRO 100 |

Store below 30°C (86°F).

CIPRO Oral Suspension is supplied in 5% and 10% strengths. The drug product is composed of two components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. See Instructions To The Pharmacist For Use/Handling.

| Strengths | Total volume after reconstitution | Ciprofloxacin Concentration | Ciprofloxacin contents per bottle | NDC Code |
|-----------|-----------------------------------|-----------------------------|-----------------------------------|--------------|
| 5% | 100 mL | 250 mg/5 mL | 5,000 mg | 0026-8551-36 |
| 10% | 100 mL | 500 mg/5 mL | 10,000 mg | 0026-8553-36 |

Microcapsules and diluent should be stored below 25°C (77°F) and protected from freezing.

Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing. A teaspoon is provided for the patient.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See WARNINGS.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystaluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystaluria is rare since human urine is typically acidic. In rhesus monkeys, crystaluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid I.V. injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyramine, an antihistamine. In rhesus monkeys, rapid I.V. injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Uncomplicated Cystitis

Two double-blind, controlled clinical studies of acute uncomplicated cystitis in women were performed in the U.S. At the 5-9 day post-therapy follow-up visit, the clinical resolution rates in the first study, which compared ciprofloxacin 100 mg BID for 3 days to ciprofloxacin 250 mg BID for 7 days, were 87% (82/94) and 94% (81/86), respectively. For *E. coli*, the bacteriological eradication rates for the first study were 91% (64/70) in the ciprofloxacin 100 mg regimen and 97% (67/69) in the ciprofloxacin 250 mg regimen. The second study's bacteriological eradication rates were 95% (117/123) for the ciprofloxacin 100 mg regimen and 98% (103/105) for the control regimen. Pooled eradication rates for the ciprofloxacin 100 mg treatment arms were 100% (16/16) for *S. saprophyticus*.

INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See DOSAGE AND ADMINISTRATION.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady-state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 µg/mL. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to pediatric patients are limited. (For additional information, see PRECAUTIONS, Pediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.⁴

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD₅₀ (~5.5 x 10⁹ spores (range 5-30 LD₅₀) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady-state ranged from 0.98 to 1.69 µg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL.⁵ Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p < 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.⁵

Instructions To The Pharmacist For Use/Handling Of CIPRO Oral Suspension:

CIPRO Oral Suspension is supplied in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent) which must be combined prior to dispensing.

One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250 mg of ciprofloxacin.

One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500 mg of ciprofloxacin.

Appropriate Dosing Volumes of the Oral Suspensions:

| Dose | 5% | 10% |
|--------|-------|--------|
| 250 mg | 5 mL | 2.5 mL |
| 500 mg | 10 mL | 5 mL |
| 750 mg | 15 mL | 7.5 mL |

Preparation of the suspension:

CIPRO Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

Instruct the patient to shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds and not to chew the microcapsules.

References:

- National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*-Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol 20, No. 2. NCCLS, Wayne, PA, January, 2000.
- National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*-Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1. NCCLS, Wayne, PA, January, 2000.
- Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Product's Advisory Committee meeting, March 31, 1993, Silver Spring, MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA. 4. 21 CFR 314.510 (Subpart H - Accelerated Approval of New Drugs for Life-Threatening Illnesses).
- Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. *J Infect Dis* 1992; 166:1184-7.
- Friedlander AM, et al. Postexposure prophylaxis against experimental inhalational anthrax. *J Infect Dis* 1993; 167:1239-42.
- Friedman J, Polkka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.
- Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluorquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother* 1998; 42(6):1336-1339.
- Schaefer C, Arnour-Elefant E, Viel T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European network of teratology information services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69:83-89.

Patient Information About:

CIPRO® (ciprofloxacin hydrochloride) TABLETS

CIPRO® (ciprofloxacin*) ORAL SUSPENSION

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO is right for you.

What is CIPRO?

CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria that can infect these areas of the body. CIPRO 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). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your condition is not improving while taking CIPRO. CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:

Unless directed otherwise by your physician, CIPRO should be taken twice a day at approximately the same time, in the morning and in the evening. CIPRO can be taken with food or on an empty stomach. CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, CIPRO may be taken with a meal that contains these products.

You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection. Do not take a double dose of CIPRO even if you miss a dose by mistake.

CIPRO Oral Suspension:

Take CIPRO Oral Suspension in the same way as above. In addition, remember to shake the bottle vigorously each time before use for approximately 15 seconds to make sure the suspension is mixed well. Be sure to swallow the required amount of suspension. Do not chew the microcapsules. Close the bottle completely after use. The product can be used for 14 days when stored in a refrigerator or at room temperature. After treatment has been completed, any remaining suspension should be discarded.

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones". CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO talk to your doctor before taking this medication.

In general, CIPRO is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO?

CIPRO is generally well tolerated. The most common side effects, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort. If diarrhea persists, call your health care professional.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including CIPRO, even after just one dose. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPRO and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO.

You should be careful about driving or operating machinery until you are sure CIPRO is not causing dizziness. Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. Be sure to let your physician know if you have a history of convulsions. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

CIPRO has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO and call your health care professional.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

CIPRO can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO.

Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from working. Other medications such as sulcrilate and Videx® (didanosine) chewable/buffered tablets or pediatric powder may also stop CIPRO from working. You should take CIPRO either 2 hours before or 6 hours after taking these products.

What if I have been prescribed CIPRO for possible anthrax exposure?

CIPRO has been approved to reduce the chance of developing anthrax infection following exposure to the anthrax bacteria. In general, CIPRO is not recommended for children; however, it is approved for use in patients younger than 18 years old for anthrax exposure. If you are pregnant, or plan to become pregnant while taking CIPRO, you and your doctor should discuss if the benefits of taking CIPRO for anthrax outweigh the risks.

CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent anthrax might be acceptable due to the seriousness of the disease. You and your doctor should discuss the risks of not taking your medicine against the risks of experiencing side effects.

CIPRO can cause dizziness, confusion, or other similar side effects in some people. Therefore, it is important to know how CIPRO affects you before driving a car or performing other activities that require you to be alert and coordinated such as operating machinery.

Your doctor has prescribed CIPRO only for you. Do not give it to other people. Do not use it for a condition for which it was not prescribed. You should take your CIPRO for as long as your doctor prescribes it; stopping CIPRO too early may result in failure to prevent anthrax.

Remember:

Do not give CIPRO to anyone other than the person for whom it was prescribed.

Take your dose of CIPRO in the morning and in the evening.

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

Keep CIPRO and all medications out of reach of children.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition".



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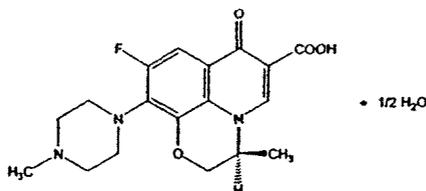
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CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy

Printed in U.S.A.

LEVAQUIN® (levofloxacin) Tablets
LEVAQUIN® (levofloxacin) Injection
LEVAQUIN® (levofloxacin in 5% dextrose) Injection
DESCRIPTION

LEVAQUIN® (levofloxacin) is a synthetic broad spectrum antibacterial agent for oral and intravenous 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:

Its empirical formula is C₁₈H₂₀FN₃O₄ • 1/2 H₂O 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.

750 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide,

polysorbate 80.

LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. LEVAQUIN Injection in Premix Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. The appearance of LEVAQUIN Injection may range from a clear yellow to a greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN Injection in Single-Use Vials contains levofloxacin in Water for Injection. LEVAQUIN Injection in Premix Flexible Containers is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D₅W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

CLINICAL PHARMACOLOGY

The mean \pm 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 in Table 1.

Absorption

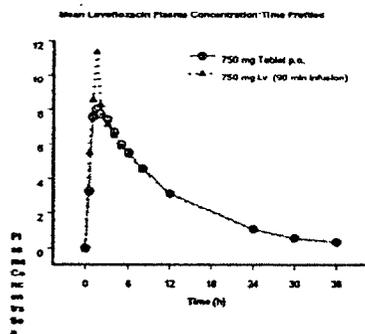
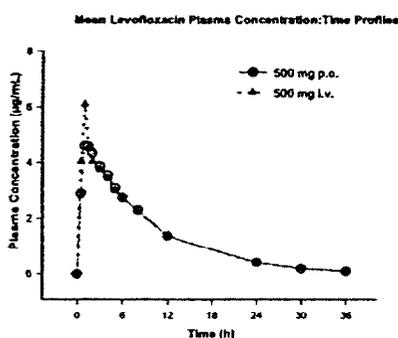
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean \pm SD peak plasma concentration attained was 6.2 ± 1.0 μ g/mL after a 500 mg dose infused over 60 minutes and 11.5 ± 4.0 μ g/mL after a 750 mg dose infused over 90 minutes.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral /or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean \pm SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ± 1.4 and 0.5 ± 0.2 μ g/mL after the 500 mg doses, and 8.6 ± 1.9 and 1.1 ± 0.4 μ g/mL after the 750 mg doses, respectively. The mean \pm SD peak and trough plasma concentrations attained following multiple

once-daily i.v. regimens were approximately 6.4 ± 0.8 and 0.6 ± 0.2 $\mu\text{g/mL}$ after the 500 mg doses, and 12.1 ± 4.1 and 1.3 ± 0.71 $\mu\text{g/mL}$ after the 750 mg doses, respectively.

Oral administration of a 500-mg LEVAQUIN tablet with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin tablets 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.)



Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin, respectively, to healthy subjects. 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 $\mu\text{g/g}$

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-ofloxacin. 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 substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50mL/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.**)

Table 1. Mean \pm SD Levofloxacin PK Parameters

| Regimen | C_{max} ($\mu\text{g/mL}$) | T_{max} (h) | AUC ($\mu\text{g}\cdot\text{h/mL}$) | CL/F^1 (mL/min) | Vd/F^1 (L) | $t_{1/2}$ (h) | CL_R (mL/min) |
|---|-----------------------------------|------------------|--|----------------------|-----------------|------------------|--------------------|
| Single dose | | | | | | | |
| 250 mg p.o. ³ | 2.8 \pm 0.4 | 1.6 \pm 1.0 | 27.2 \pm 3.9 | 156 \pm 20 | ND | 7.3 \pm 0.9 | 142 \pm 21 |
| 500 mg p.o. ^{3*} | 5.1 \pm 0.8 | 1.3 \pm 0.6 | 47.9 \pm 6.8 | 178 \pm 28 | ND | 6.3 \pm 0.6 | 103 \pm 30 |
| 500 mg i.v. ³ | 6.2 \pm 1.0 | 1.0 \pm 0.1 | 48.3 \pm 5.4 | 175 \pm 20 | 90 \pm 11 | 6.4 \pm 0.7 | 112 \pm 25 |
| 750 mg p.o. ^{5*} | 9.3 \pm 1.6 | 1.6 \pm 0.8 | 101 \pm 20 | 129 \pm 24 | 83 \pm 17 | 7.5 \pm 0.9 | ND |
| 750 mg i.v. ⁵ | 11.5 \pm 4.0 | ND | 110 \pm 40 | 126 \pm 39 | 75 \pm 13 | 7.5 \pm 1.6 | ND |
| Multiple dose | | | | | | | |
| 500 mg q24h p.o. ³ | 5.7 \pm 1.4 | 1.1 \pm 0.4 | 47.5 \pm 6.7 | 175 \pm 25 | 102 \pm 22 | 7.6 \pm 1.6 | 116 \pm 31 |
| 500 mg q24h i.v. ³ | 6.4 \pm 0.8 | ND | 54.6 \pm 11.1 | 158 \pm 29 | 91 \pm 12 | 7.0 \pm 0.8 | 99 \pm 28 |
| 500 mg or 250 mg q24h i.v., patients with bacterial infection ⁶ | 8.7 \pm 4.0 ⁷ | ND | 72.5 \pm 51.2 ⁷ | 154 \pm 72 | 111 \pm 58 | ND | ND |
| 750 mg q24h p.o. ³ | 8.6 \pm 1.9 | 1.4 \pm 0.5 | 90.7 \pm 17.6 | 143 \pm 29 | 100 \pm 16 | 8.8 \pm 1.5 | 116 \pm 28 |
| 750 mg q24h i.v. ⁵ | 12.1 \pm 4.1 ⁴ | ND | 108 \pm 34 | 126 \pm 37 | 80 \pm 27 | 7.9 \pm 1.9 | ND |
| 500 mg p.o. single dose, effects of gender and age: | | | | | | | |
| Male ⁸ | 5.5 \pm 1.1 | 1.2 \pm 0.4 | 54.4 \pm 18.9 | 166 \pm 44 | 89 \pm 13 | 7.5 \pm 2.1 | 126 \pm 38 |
| Female ⁹ | 7.0 \pm 1.6 | 1.7 \pm 0.5 | 67.7 \pm 24.2 | 136 \pm 44 | 62 \pm 16 | 6.1 \pm 0.8 | 106 \pm 40 |
| Young ¹⁰ | 5.5 \pm 1.0 | 1.5 \pm 0.6 | 47.5 \pm 9.8 | 182 \pm 35 | 83 \pm 18 | 6.0 \pm 0.9 | 140 \pm 33 |
| Elderly ¹¹ | 7.0 \pm 1.6 | 1.4 \pm 0.5 | 74.7 \pm 23.3 | 121 \pm 33 | 67 \pm 19 | 7.6 \pm 2.0 | 91 \pm 29 |
| 500 mg p.o. single dose, patients with renal insufficiency: | | | | | | | |
| CL_{CR} 50-80 mL/min | 7.5 \pm 1.8 | 1.5 \pm 0.5 | 95.6 \pm 11.8 | 88 \pm 10 | ND | 9.1 \pm 0.9 | 57 \pm 8 |
| CL_{CR} 20-49 mL/min | 7.1 \pm 3.1 | 2.1 \pm 1.3 | 182.1 \pm 62.6 | 51 \pm 19 | ND | 27 \pm 10 | 26 \pm 13 |
| CL_{CR} <20 mL/min | 8.2 \pm 2.6 | 1.1 \pm 1.0 | 263.5 \pm 72.5 | 33 \pm 8 | ND | 35 \pm 5 | 13 \pm 3 |
| Hemodialysis | 5.7 \pm 1.0 | 2.8 \pm 2.2 | ND | ND | ND | 76 \pm 42 | ND |
| CAPD | 6.9 \pm 2.3 | 1.4 \pm 1.1 | ND | ND | ND | 51 \pm 24 | ND |

¹ clearance/bioavailability

² volume of distribution/bioavailability

³ healthy males 18-53 years of age

⁴ 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

⁵ healthy male and female subjects 18-54 years of age

⁶ 500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin

⁷ dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

⁸ healthy males 22-75 years of age

⁹ healthy females 18-80 years of age

¹⁰ young healthy male and female subjects 18-36 years of age

¹¹ healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; $F = 0.99 \pm 0.08$ from a 500-mg tablet and $F = 0.99 \pm 0.06$ from a 750-mg tablet; 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 bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes 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, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β -lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

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 (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including penicillin-resistant strains*)

Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of —
2 μ g/mL

Aerobic gram-negative microorganisms

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

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 values) of 2 µg/mL or less against most (≥90%) 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 haemolyticus

Streptococcus (Group C/F)

Streptococcus (Group G)

Streptococcus agalactiae

Streptococcus milleri

Viridans group streptococci

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter (diversus) koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea (Enterobacter) agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values 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 levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa*:

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤2 | Susceptible (S) |
| 4 | Intermediate (I) |
| ≥8 | Resistant (R) |

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*.^a

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤2 | Susceptible (S) |

^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* spp. including *S. pneumoniae*.^b

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤2 | Susceptible (S) |
| 4 | Intermediate (I) |
| ≥8 | Resistant (R) |

^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:

| <u>Microorganism</u> | | <u>MIC (µg/mL)</u> |
|---------------------------------|-------------------------|--------------------|
| <i>Enterococcus faecalis</i> | ATCC 29212 | 0.25 – 2 |
| <i>Escherichia coli</i> | ATCC 25922 | 0.008 - 0.06 |
| <i>Escherichia coli</i> | ATCC 35218 | 0.015 - 0.06 |
| <i>Haemophilus influenzae</i> | ATCC 49247 ^c | 0.008 - 0.03 |
| <i>Pseudomonas aeruginosa</i> | ATCC 27853 | 0.5 – 4 |
| <i>Staphylococcus aureus</i> | ATCC 29213 | 0.06 - 0.5 |
| <i>Streptococcus pneumoniae</i> | ATCC 49619 ^d | 0.5 – 2 |

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

^d 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 procedure² 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 testing *Enterobacteriaceae*, Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa*:

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥17 | Susceptible (S) |
| 14-16 | Intermediate (I) |
| ≤13 | Resistant (R) |

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:^e

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥17 | Susceptible (S) |

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

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* spp. including *S. pneumoniae*.^f

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥17 | Susceptible (S) |
| 14-16 | Intermediate (I) |
| ≤13 | Resistant (R) |

^f These zone diameter standards for *Streptococcus* spp. including *S. 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:

| <u>Microorganism</u> | <u>Zone Diameter</u> <u>(mm)</u> |
|---|-------------------------------------|
| <i>Escherichia coli</i> ATCC 25922 | 29 - 37 |
| <i>Haemophilus influenzae</i> ATCC 49247 ^g | 32 - 40 |
| <i>Pseudomonas aeruginosa</i> ATCC 27853 | 19 - 26 |
| <i>Staphylococcus aureus</i> ATCC 25923 | 25 - 30 |
| <i>Streptococcus pneumoniae</i> ATCC 49619 ^h | 20 - 25 |

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

^h 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

LEVAQUIN Tablets/Injection 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. LEVAQUIN Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

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.

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β -lactam is recommended. (See **CLINICAL STUDIES**.)

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin $\geq 2 \mu\text{g/mL}$), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES**.)

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis*.

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

Chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or *Staphylococcus epidermidis*.

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 PEDIATRIC PATIENTS, 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. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. 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

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION**.)

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 <50 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**.)

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided.

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 multivitamin preparations with zinc or Videx[®] (didanosine), chewable/buffered tablets or the pediatric powder for oral solution should be taken at least two hours before or two hours after oral levofloxacin administration. (See **Drug Interactions**);
- that oral 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**.);
- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin.
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Tablets: 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 multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx[®] (didanosine), chewable/buffered tablets or the pediatric powder for oral solution may substantially 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.

LEVAQUIN Injection: There are no data concerning an interaction of **intravenous** quinolones with **oral** antacids, sucralfate, multivitamins, Videx[®] (didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND 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. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

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_{max} and k_e were slightly lower while T_{max} and $t_{1/2}$ 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 $t_{1/2}$ 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 lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 µg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 µg/g at C_{max}.

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/TU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of

810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

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 pediatric patients 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.)

Geriatric Use

In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥ 65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials

conducted in North America was ~~6.2%~~ 6.3%. Among patients receiving levofloxacin therapy, ~~4.1%~~ 4.0% discontinued levofloxacin therapy due to adverse experiences. The overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily compared to patients receiving doses from 250 mg once daily to 500 mg twice daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:

nausea 1.3%, diarrhea 1.0%, vaginitis ~~0.7%~~ 0.8% insomnia 0.4%, abdominal pain ~~0.4%~~ 0.5%, flatulence 0.3%, pruritus 0.3%, dizziness 0.3%, dyspepsia 0.3%, rash 0.3%, genital moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%, injection site pain 0.2%, injection site reaction 0.2%, injection site inflammation 0.1%, constipation 0.1%, fungal infection 0.1%, genital pruritis 0.1%, headache 0.1%, moniliasis 0.1%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, maculopapular rash 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:

nausea 7.0%, headache 6.1%, diarrhea 5.7%, insomnia ~~4.5%~~ 4.3%, ~~injection site reaction 3.5%~~, constipation 3.3%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

dizziness ~~2.6%~~ 2.5%, abdominal pain ~~2.5%~~ 2.6% dyspepsia 2.3%, vomiting ~~2.4%~~ 2.3%, vaginitis 1.8%, ~~injection site pain 1.7%~~, flatulence 1.4%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain ~~1.2%~~ 1.1%, fatigue 1.3%, rash 1.4%, back pain 1.1%, ~~injection site inflammation 1.1%~~, rhinitis ~~1.0%~~ 1.1%, ~~taste perversion 1.0%~~, dyspnea 1.1%, pharyngitis 1.0%.

In clinical trials, the following events, of potential medical importance, occurred at a rate of 0.1% to 1.0%, regardless of drug relationship:

Autonomic Nervous System Disorders:
Body as a Whole –
General Disorders:

Postural hypotension

Asthenia, fever, malaise, rigors, substernal chest pain, syncope, enlarged abdomen, allergic reaction, ~~headache~~, hot flashes, edema, influenza-like symptoms, leg pain, multiple organ failure, condition aggravated, peripheral edema

Cardiovascular Disorders,
General:

Cardiac failure, circulatory failure, hypertension, hypotension, postural hypotension

| | |
|--|--|
| Central and Peripheral Nervous System Disorders: | Abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, <u>ataxia, migraine</u> |
| Gastro-Intestinal System Disorders: | Dry mouth, dysphagia, gastroenteritis, G.I. hemorrhage, pancreatitis, pseudomembranous colitis, tongue edema, gastritis, gastroesophageal reflux, melena, esophagitis, stomatitis, <u>intestinal obstruction</u> |
| Hearing and Vestibular Disorders: | Earache, tinnitus |
| Heart Rate and Rhythm Disorders: | Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia, <u>heart block, ventricular fibrillation</u> |
| Liver and Biliary System Disorders: | <u>Elevated bilirubin</u> , Abnormal hepatic function, cholelithiasis, jaundice, hepatic failure, <u>hepatic coma, bilirubinemia</u> |
| Metabolic and Nutritional Disorders: | Hypomagnesemia, thirst, aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, <u>gout, hypernatremia, hypophosphatemia, increased LDH, weight decrease, fluid overload, electrolyte abnormality</u> |
| Musculo-Skeletal System Disorders: | Arthralgia, arthritis, arthrosis, pathological fracture, myalgia, osteomyelitis, synovitis, tendonitis, <u>muscle weakness, rhabdomyolysis, skeletal pain</u> |
| Myo, Endo, Pericardial and Valve Disorders: | Angina pectoris, myocardial infarction, <u>coronary thrombosis</u> |
| Neoplasms: | Carcinoma |
| Other Special Senses Disorders: | Parosmia, taste perversion |
| Platelet, Bleeding and Clotting Disorders: | Pulmonary embolism, hematoma, epistaxis, purpura, thrombocytopenia, <u>abnormal platelets, embolism (blood clot)</u> |
| Psychiatric Disorders: | Abnormal dreaming, agitation, anorexia, anxiety, confusion, depression, hallucination, nervousness, paranoia, sleep disorder, somnolence, <u>aggressive reaction, delirium, emotional lability, impaired concentration, impotence, manic reaction, mental deficiency, withdrawal syndrome</u> |
| Red Blood Cell Disorders: | Anemia |
| Reproductive Disorders: | Dysmenorrhea, leukorrhea, <u>ejaculation failure</u> |
| Resistance Mechanism Disorders: | Abscess, herpes simplex, bacterial infection, viral infection, moniliasis, otitis media, sepsis, fungal infection, <u>genital moniliasis</u> |
| Respiratory System Disorders: | Bronchitis, epistaxis, pharyngitis, rhinitis , upper respiratory tract infection, asthma, coughing, dyspnea, hemoptysis, hypoxia, pleural effusion, respiratory insufficiency, <u>airway obstruction, ARDS, aspiration, bronchospasm, emphysema, pneumonia, pneumothorax, pulmonary collapse, pulmonary edema, respiratory depression, respiratory disorder</u> |
| Skin and Appendages Disorders: | Rash, <u>Dry skin</u> , genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration, urticaria, <u>bullous eruption, erythematous rash, maculopapular rash, alopecia, eczema</u> |

| | |
|------------------------------------|---|
| Urinary System Disorders: | Urinary tract infection, abnormal renal function, acute renal failure, hematuria, <u>face edema, dysuria, oliguria, urinary incontinence, urinary retention</u> |
| Vascular (Extracardiac) Disorders: | Cerebrovascular disorder, phlebitis, purpura, thrombophlebitis (deep), <u>flushing, gangrene</u> |
| Vision Disorders: | Abnormal vision, conjunctivitis, <u>diplopia, eye pain</u> |
| White Cell and RES Disorders: | Granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal (not otherwise specified), <u>leukopenia</u> |

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 markedly abnormal laboratory values appeared in >2% 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 (2.2%)

Hematology: decreased lymphocytes (2.4% 2.3%)

It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

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, increased International Normalized Ratio (INR)/prothrombin time, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

OVERDOSAGE

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 overdose, 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

LEVAQUIN Injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. (See **PRECAUTIONS**.)

Single-use vials require dilution prior to administration. (See PREPARATION FOR ADMINISTRATION.)

The usual dose of LEVAQUIN Tablets or Injection is 250 mg or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours or 750 mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance > 80 mL/min). For patients with altered renal function 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, 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.

Patients with Normal Renal Function

| Infection* | Unit Dose | Freq. | Duration** | Daily Dose |
|--|---------------|-------------|----------------|---------------|
| Acute Bacterial Exacerbation of Chronic Bronchitis | 500 mg | q24h | 7 days | 500 mg |
| Nosocomial Pneumonia | 750 mg | q24h | 7-14 days | 750 mg |
| Comm. Acquired Pneumonia | 500 mg | q24h | 7-14 days | 500 mg |
| Acute Maxillary Sinusitis | 500 mg | q24h | 10-14 days | 500 mg |
| Complicated SSSI | 750 mg | q24h | 7-14 days | 750 mg |
| Uncomplicated SSSI | 500 mg | q24h | 7-10 days | 500 mg |
| <u>Chronic Bacterial Prostatitis</u> | <u>500 mg</u> | <u>q24h</u> | <u>28 days</u> | <u>500 mg</u> |
| Complicated UTI | 250 mg | q24h | 10 days | 250 mg |
| Acute pyelonephritis | 250 mg | q24h | 10 days | 250 mg |
| Uncomplicated UTI | 250 mg | q24h | 3 days | 250 mg |

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

** Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

Patients with Impaired Renal Function

| Renal Status | Initial Dose | Subsequent Dose |
|--|-------------------------------|-----------------|
| Acute Bacterial Exacerbation of Chronic Bronchitis / Comm. Acquired Pneumonia / Acute Maxillary Sinusitis / Uncomplicated SSSI/<u>Chronic Bacterial Prostatitis</u> | | |
| CL _{CR} from 50 to 80 mL/min | No dosage adjustment required | |
| CL _{CR} from 20 to 49 mL/min | 500 mg | 250 mg q24h |
| CL _{CR} from 10 to 19 mL/min | 500 mg | 250 mg q48h |
| Hemodialysis | 500 mg | 250 mg q48h |
| CAPD | 500 mg | 250 mg q48h |
| Complicated SSSI/Nosocomial Pneumonia | | |
| CL _{CR} from 50 to 80 mL/min | No dosage adjustment required | |
| CL _{CR} from 20 to 49 mL/min | 750 mg | 750 mg q48h |
| CL _{CR} from 10 to 19 mL/min | 750 mg | 500 mg q48h |
| Hemodialysis | 750 mg | 500 mg q48h |
| CAPD | 750 mg | 500 mg q48h |
| Complicated UTI / Acute Pyelonephritis | | |
| CL _{CR} ≥20 mL/min | No dosage adjustment required | |
| CL _{CR} from 10 to 19 mL/min | 250 mg | 250 mg q48h |
| Uncomplicated UTI | | |
| No dosage adjustment required | | |

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) =

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

72 x serum creatinine (mg/dL)

Women: 0.85 x the value calculated for men.

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

Preparation of Levofloxacin Injection for Administration

LEVAQUIN Injection in Single-Use Vials: LEVAQUIN Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION.** (See **COMPATIBLE INTRAVENOUS SOLUTIONS.**) The concentration of the resulting diluted solution should be

5 mg/mL prior to administration.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. **Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use. (See Stability of LEVAQUIN Injection Following Dilution.)**

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Prepare the desired dosage of levofloxacin according to the following chart:

| Desired Dosage Strength | From Appropriate Vial, Withdraw Volume | Volume of Diluent | Infusion Time |
|-------------------------|--|-------------------|---------------|
| 250 mg | 10 mL (20 mL Vial) | 40 mL | 60 min |
| 500 mg | 20 mL (20 mL Vial) | 80 mL | 60 min |
| 750 mg | 30 mL (30 mL Vial) | 120 mL | 90 min |

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

Compatible Intravenous Solutions: Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Intravenous Fluids

Final pH of
LEVAQUIN Solution

| | |
|---|------|
| 0.9% Sodium Chloride Injection, USP | 4.71 |
| 5% Dextrose Injection, USP | 4.58 |
| 5% Dextrose/0.9% NaCl Injection | 4.62 |
| 5% Dextrose in Lactated Ringers | 4.92 |
| Plasma-Lyte® 56/5% Dextrose Injection | 5.03 |
| 5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection | 4.61 |
| Sodium Lactate Injection (M/6) | 5.54 |

LEVAQUIN Injection Premix in Single-Use Flexible Containers: LEVAQUIN Injection is also supplied in flexible containers containing a premixed, ready-to-use levofloxacin solution in D₅W for single-use. The fill volume is either 50 or 100 mL for the 100 mL flexible container or 150 mL for the 150 mL container. **NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY.** Consequently each 50 mL, 100 mL, and 150 mL premix flexible container already contains a dilute solution with the equivalent of 250 mg, 500 mg, and 750 mg of levofloxacin, respectively (5 mg/mL) in 5% Dextrose (D₅W).

This parenteral drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in flexible containers or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the Use of LEVAQUIN Injection Premix in Flexible Containers

To open:

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.
3. Do not use if the solution is cloudy or a precipitate is present.
4. Use sterile equipment.

5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. **NOTE: See full directions on administration set carton.**
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN Injection in Premix Flexible Containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

Stability of LEVAQUIN Injection as Supplied

When stored under recommended conditions, LEVAQUIN Injection, as supplied in 20 mL and 30 mL vials, or 100 mL and 150 mL flexible containers, is stable through the expiration date printed on the label.

Stability of LEVAQUIN Injection Following Dilution

LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at -20°C (-4°F). **THAW FROZEN SOLUTIONS AT ROOM TEMPERATURE 25°C (77°F) OR IN A REFRIGERATOR 8°C (46°F). DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

HOW SUPPLIED

LEVAQUIN Tablets

LEVAQUIN (levofloxacin) Tablets are supplied as 250, 500, and 750 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: "LEVAQUIN" 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: "LEVAQUIN" on side 1 and "500" on side 2

bottles of 50 (NDC 0045-1525-50)

unit-dose/100 tablets (NDC 0045-1525-10)

750 mg tablets: color: white

debossing: "LEVAQUIN" on side 1 and "750" on side 2

bottles of 50 (NDC 0045-1530-50)

unit-dose/100 tablets (NDC 0045-1530-10)

LEVAQUIN Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN Tablets are manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

LEVAQUIN Injection

Single-Use Vials: LEVAQUIN (levofloxacin) Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

25 mg/mL, 20 mL vials (NDC 0045-0069-51)

25 mg/mL, 30 mL vials (NDC 0045-0065-55)

LEVAQUIN Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

LEVAQUIN Injection in Single-Use Vials is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by OMJ Pharmaceuticals, Inc., San German, Puerto

Rico, 00683.

Premix in Flexible Containers: LEVAQUIN (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D₅W).

5 mg/mL (250 mg), 50 mL flexible container (NDC 0045-0067-01)

5 mg/mL (500 mg), 100 mL flexible container (NDC 0045-0068-01)

5 mg/mL (750 mg), 150 mL flexible container (NDC 0045-0066-01)

LEVAQUIN Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light.

LEVAQUIN Injection Premix in Flexible Containers is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by ABBOTT Laboratories, North Chicago, IL 60064.

CLINICAL STUDIES

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7-15 days to intravenous imipenem/cilastatin (500-1000mg q6-8 hours daily) followed by oral ciprofloxacin (750 mg q12 hours daily) for a total of 7-15 days. Levofloxacin-treated patients received an average of 7 days of intravenous therapy (range: 1-16 days); comparator-treated patients received an average of 8 days intravenous therapy (range 1-19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3-15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen were as follows:

| Pathogen | Levofloxacin | | Imipenem/Cilastatin | |
|-----------------------------------|--------------|--|---------------------|--|
| | N | <u>No. (%) of Patients</u> Microbiologic / Clinical Outcomes | N | <u>No. (%) of Patients</u> Microbiologic / Clinical Outcomes |
| <i>MSSA</i> ^a | 21 | 14 (66.7) / 13 (61.9) | 19 | 13 (68.4) / 15 (78.9) |
| <i>P. aeruginosa</i> ^b | 17 | 10 (58.8) / 11 (64.7) | 17 | 5 (29.4) / 7 (41.2) |
| <i>S. marcescens</i> | 11 | 9 (81.8) / 7 (63.6) | 7 | 2 (28.6) / 3 (42.9) |
| <i>E. coli</i> | 12 | 10 (83.3) / 7 (58.3) | 11 | 7 (63.6) / 8 (72.7) |
| <i>K. pneumoniae</i> ^c | 11 | 9 (81.8) / 5 (45.5) | 7 | 6 (85.7) / 3 (42.9) |
| <i>H. influenzae</i> | 16 | 13 (81.3) / 10 (62.5) | 15 | 14 (93.3) / 11 (73.3) |
| <i>S. pneumoniae</i> | 4 | 3 (75.0) / 3 (75.0) | 7 | 5 (71.4) / 4 (57.1) |

^a Methicillin-susceptible *S. aureus*.

^b See above text for use of combination therapy.

^c The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study.

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, multicenter, 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%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative 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:

| <u>Pathogen</u> | <u>No.</u> <u>Pathogens</u> | <u>Microbiologic</u> <u>Eradication Rate (%)</u> |
|--------------------------|--------------------------------|---|
| <i>H. influenzae</i> | 55 | 98 |
| <i>S. pneumoniae</i> | 83 | 95 |
| <i>S. aureus</i> | 17 | 88 |
| <i>M. catarrhalis</i> | 18 | 94 |
| <i>H. parainfluenzae</i> | 19 | 95 |
| <i>K. pneumoniae</i> | 10 | 100.0 |

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC value for penicillin —2 µg/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and three open label non-comparative studies. The total number of clinically evaluable patients with *S. pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated

patients with *S. pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (MIC value for penicillin —2 µg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe.

Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either levofloxacin 750mg QD (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the levofloxacin and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the levofloxacin treated patients and 44% of the comparator treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2-5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB₃) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5-18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented below:

| | Levofloxacin (N=136) | | Ciprofloxacin (=125) | |
|-------------------------------|----------------------|--------------------|----------------------|--------------------|
| <u>Pathogen</u> | <u>N</u> | <u>Eradication</u> | <u>N</u> | <u>Eradication</u> |
| <u><i>E. coli</i></u> | 15 | 14 (93.3%) | 11 | 9 (81.8%) |
| <u><i>E. faecalis</i></u> | 54 | 39 (72.2%) | 44 | 33 (75.0%) |
| <u>*<i>S. epidermidis</i></u> | 11 | 9 (81.8%) | 14 | 11 (78.6%) |

*Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5-18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24-45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin).

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.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically ~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7 ~~A5~~ A6, Vol. ~~20~~ 23, No. 2, NCCLS, Wayne, PA, January, ~~2000~~ 2003.
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[ADD LOGO]
OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey, USA 08869

Revised May 2003

(FINAL: 18-DEC-1997)
 [insert package insert code here]
TROVAN™ Tablets
 (trovafloxacin mesylate)
TROVAN™ I.V.
 (alatrofloxacin mesylate injection)
 For Intravenous Infusion

DEC 18 1997

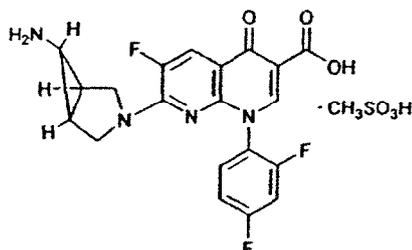
APPROVED

TROVAN is available as TROVAN Tablets (trovafloxacin mesylate) for oral administration and as TROVAN I.V. (alatrofloxacin mesylate injection), a prodrug of trovafloxacin, for intravenous administration.

DESCRIPTION**TROVAN Tablets**

TROVAN Tablets contain trovafloxacin mesylate, a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

The chemical structure is:



Its empirical formula is $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$ and its molecular weight is 512.46.

Trovafloxacin mesylate is a white to off-white powder.

Trovafloxacin mesylate is available in 100 mg and 200 mg (trovafloxacin equivalent) blue, film-coated tablets. TROVAN Tablets contain microcrystalline cellulose, crosslinked sodium carboxymethylcellulose and magnesium stearate. The tablet coating is a mixture of hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and FD&C blue #2 aluminum lake.

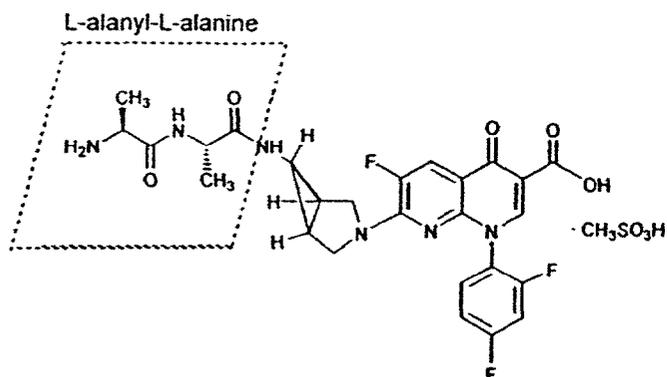
TROVAN I.V.

TROVAN I.V. contains alatrofloxacin mesylate, the L-alanyl-L-alanyl prodrug of trovafloxacin mesylate. Chemically, alatrofloxacin mesylate is (1 α , 5 α , 6 α)-L-alanyl-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate. It is intended for administration by intravenous infusion.

Following intravenous administration, the alanine substituents in alatrofloxacin are rapidly hydrolyzed *in vivo* to yield trovafloxacin. (See **CLINICAL PHARMACOLOGY**)

The chemical structure is:

47



48

49

Its empirical formula is C₂₆H₂₅F₃N₆O₅ • CH₃SO₃H and its molecular weight is 654.62.

50

Alatrofloxacin mesylate is a white to light yellow powder.

51

52

53

54

55

56

TROVAN I.V. is available in 40 mL and 60 mL single use vials as a sterile, preservative-free aqueous concentrate of 5 mg trovafloxacin/mL as alatrofloxacin mesylate intended for dilution prior to intravenous administration of doses of 200 mg or 300 mg of trovafloxacin, respectively. (See HOW SUPPLIED.)

57

58

59

60

The formulation contains Water for Injection, and may contain sodium hydroxide or hydrochloric acid for pH adjustment.

The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

61

CLINICAL PHARMACOLOGY

62

63

64

65

After intravenous administration, alatrofloxacin is rapidly converted to trovafloxacin. Plasma concentrations of alatrofloxacin are below quantifiable levels within 5 to 10 minutes of completion of a one hour infusion.

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67

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71

Absorption

Trovafloxacin is well-absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 88%. For comparable dosages, no dosage adjustment is necessary when switching from parenteral to oral administration (Figure 1). (See DOSAGE AND ADMINISTRATION.)

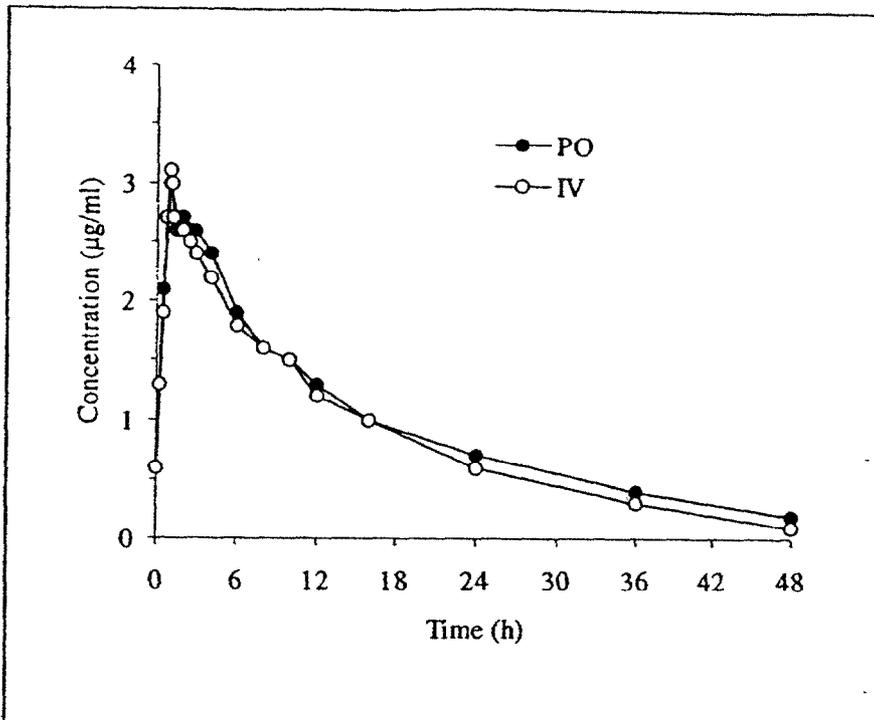


Figure 1. Mean trovafloxacin serum concentrations determined following 1 hour intravenous infusions of alatrofloxacin at daily doses of 200 mg (trovafloxacin equivalents) to healthy male volunteers and following daily oral administration of 200 mg trovafloxacin for seven days to six male and six female healthy young volunteers.

Pharmacokinetics

The mean pharmacokinetic parameters (\pm SD) of trovafloxacin after single and multiple 100 mg and 200 mg oral doses and one hour intravenous infusions of alatrofloxacin in doses of 200 and 300 mg (trovafloxacin equivalents) appear in the chart below.

| TROVAFLOXACIN PHARMACOKINETIC PARAMETERS | | | | | | | |
|--|-----------|-----------|--------------------|-----------|-----------|------------|-----------------|
| | C_{max} | T_{max} | AUC ^{1,2} | $T_{1/2}$ | V_{dss} | CL | CL _r |
| | (µg/mL) | (hrs) | (µg·h/mL) | (hrs) | (L/Kg) | (mL/hr/Kg) | (mL/hr/Kg) |
| Trovafloxacin 100 mg | | | | | | | |
| Single dose | 1.0±0.3 | 0.9±0.4 | 11.2±2.2 | 9.1 | — | — | — |
| Multiple dose | 1.1±0.2 | 1.0±0.5 | 11.8±1.8 | 10.5 | — | — | — |
| Trovafloxacin 200 mg | | | | | | | |
| Single dose | 2.1±0.5 | 1.8±0.9 | 26.7±7.5 | 9.6 | — | — | — |
| Multiple dose | 3.1±1.0 | 1.2±0.5 | 34.4±5.7 | 12.2 | — | — | — |
| Alatrofloxacin 200 mg* | | | | | | | |
| Single dose | 2.7±0.4 | 1.0±0.0 | 28.1±5.1 | 9.4 | 1.2±0.2 | 93.0±17.4 | 6.5±3.5 |
| Multiple dose | 3.1±0.6 | 1.0±0.0 | 32.2±7.3 | 11.7 | 1.3±0.1 | 81.7±17.8 | 8.6±2.4 |
| Alatrofloxacin 300 mg* | | | | | | | |
| Single dose | 3.6±0.6 | 1.3±0.4 | 46.1±5.2 | 11.2 | 1.2±0.1 | 84.6±6.0 | 6.9±0.5 |
| Multiple dose | 4.4±0.6 | 1.2±0.2 | 46.3±3.9 | 12.7 | 1.4±0.1 | 84.5±11.1 | 8.4±1.8 |

*trovafloxacin equivalents

^{1,2} Single dose: AUC(0-∞), multiple dose: AUC(0-24)

C_{max} = Maximum serum concentration; T_{max} = Time to C_{max} ; AUC = Area under concentration vs. time curve; $T_{1/2}$ = serum half-life; V_{dss} = Volume of distribution; CL = Total clearance; CL_r = Renal clearance

Serum concentrations of trovafloxacin are dose-proportional after oral administration of trovafloxacin in the dose range of 30 to 1000 mg or after intravenous administration of

88 alatrofloxacin in the dose range of 30 to 400 mg (trovafloxacin equivalents). Steady state
89 concentrations are achieved by the third daily oral or intravenous dose of trovafloxacin with
90 an accumulation factor of approximately 1.3 times the single dose concentrations.
91
92 Oral absorption of trovafloxacin is not altered by concomitant food intake; therefore, it can
93 be administered without regard to food.
94
95 The systemic exposure to trovafloxacin ($AUC_{0-\infty}$) administered as crushed tablets via
96 nasogastric tube into the stomach was identical to that of orally administered intact tablets.
97 Administration of concurrent enteral feeding solutions had no effect on the absorption of
98 trovafloxacin given via nasogastric tube into the stomach. When trovafloxacin was
99 administered as crushed tablets into the duodenum via nasogastric tube, the $AUC_{0-\infty}$ and
100 peak serum concentration (C_{max}) were reduced by 30% relative to the orally administered
101 intact tablets. Time to peak serum level (T_{max}) was also decreased from 1.7 hrs to 1.1
102 hrs..
103

104 **Distribution**

105 The mean plasma protein bound fraction is approximately 76%, and is concentration-
 106 independent. Trovafloxacin is widely distributed throughout the body. Rapid distribution of
 107 trovafloxacin into tissues results in significantly higher trovafloxacin concentrations in most
 108 target tissues than in plasma or serum.

| 109 | <u>Fluid or Tissue</u> | Tissue-Fluid/ Serum Ratio* (Range) |
|-----|-------------------------------------|---------------------------------------|
| 110 | <u>Respiratory</u> | |
| 111 | bronchial macrophages | |
| 112 | (multiple dose) | 24.1 (9.6-41.8) |
| 113 | lung mucosa | 1.1(0.7-1.5) |
| 114 | lung epithelial lining fluid | |
| 115 | (multiple dose) | 5.8 (1.1-17.5) |
| 116 | whole lung | 2.1 (0.42-5.03) |
| 117 | | |
| 118 | <u>Skin, Musculoskeletal</u> | |
| 119 | skin | 1.0 (0.20-1.88) |
| 120 | subcutaneous tissue | 0.4 (0.15-0.68) |
| 121 | skin blister fluid | 0.7-0.9 (blister/plasma) |
| 122 | skeletal muscle | 1.5 (0.50-2.90) |
| 123 | bone | 1.0 (0.55-1.67) |
| 124 | | |
| 125 | <u>Gastrointestinal</u> | |
| 126 | colonic tissue | 0.7 (0.0-1.47) |
| 127 | peritoneal fluid | 0.4 (0.0-1.25) |
| 128 | bile | 15.4 (11.9-21.0) |
| 129 | | |
| 130 | <u>Central Nervous System</u> | |
| 131 | cerebrospinal fluid (CSF), adults | 0.25 (0.03-0.33) |
| 132 | cerebrospinal fluid (CSF), children | 0.28** |
| 133 | | |
| 134 | <u>Reproductive</u> | |
| 135 | prostatic tissue | 1.0 (0.5-1.6) |
| 136 | cervix (multiple dose) | 0.6 (0.5-0.7) |
| 137 | ovary | 1.6 (0.3-2.2) |
| 138 | fallopian tube | 0.7 (0.2-1.1) |
| 139 | myometrium (multiple dose) | 0.6 (0.4-0.8) |
| 140 | uterus | 0.6 (0.3-0.8) |
| 141 | vaginal fluid (multiple dose) | 4.7 (0.8-20.8) |
| 142 | | |
| 143 | | |
| 144 | | |
| 145 | | |

146 * Mean values in adults over 2-29 hours following drug administration, except individual lung tissues, which were
 147 single time points of 6 hours following drug administration

148 ** Ratio of composite AUC(0-24) in CSF/composite AUC(0-24) in serum in 22 pediatric patients aged 1 to 12
 149 years after 1 hour i.v. infusion of single dose alatrofloxacin (equivalent trovafloxacin dose range: 4.5-9.9 mg/kg)

150

151 Presence in Breast Milk

152 Trovafloxacin was found in measurable concentrations in the breast milk of three lactating
153 subjects. The average measurable breast milk concentration was 0.8 µg/mL (range: 0.3-2.1
154 µg/mL) after single i.v. alatrofloxacin (300 mg trovafloxacin equivalents) and repeated oral
155 trovafloxacin (200 mg) doses.

156

157 Metabolism

158

159 Trovafloxacin is metabolized by conjugation (the role of cytochrome P₄₅₀ oxidative
160 metabolism of trovafloxacin is minimal). Thirteen percent of the administered dose appears
161 in the urine in the form of the ester glucuronide and 9% appears in the feces as the N-acetyl
162 metabolite (2.5% of the dose is found in the serum as the active N-acetyl metabolite). Other
163 minor metabolites (diacid, sulfamate, hydroxycarboxylic acid) have been identified in both
164 urine and feces in small amounts (<4% of the administered dose)..

165

166 Excretion

167 Approximately 50% of an oral dose is excreted unchanged (43 % in the feces and 6% in the
168 urine).

169

170 After multiple 200 mg doses, to healthy subjects, mean (± SD) cumulative urinary
171 trovafloxacin concentrations were 12.1 ±3.4 µg/mL. With these levels of trovafloxacin in
172 urine, crystals of trovafloxacin have not been observed in the urine of human subjects.

173

174 Special Populations

175

176 Geriatric

177 In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age (range 19-78
178 years).

179

180 Pediatric

181 Limited information is available in the pediatric population (See **Distribution**). The
182 pharmacokinetics of trovafloxacin have not been fully characterized in pediatric populations
183 less than 18 years of age.

184

185 Gender

186 There are no significant differences in trovafloxacin pharmacokinetics between males and
187 females when differences in body weight are taken into account. After single 200 mg doses,
188 trovafloxacin C_{max} and AUC(0-∞) were 60% and 32% higher, respectively, in healthy
189 females compared to healthy males. Following repeated daily administration of 200 mg for
190 7 days, the C_{max} for trovafloxacin was 38% higher and AUC(0-24) was 16% higher in
191 healthy females compared to healthy males. The clinical importance of the increases in
192 serum levels of trovafloxacin in females has not been established. (See **PRECAUTIONS:**
193 **Information for Patients**).

194

195 Chronic Hepatic Disease

196 Following repeated administration of 100 mg for 7 days to patients with mild cirrhosis (Child-
197 Pugh Class A), the AUC(0-24) for trovafloxacin was increased ~45% compared to matched
198 controls. Repeated administration of 200 mg for 7 days to patients with moderate cirrhosis
199 (Child-Pugh Class B) resulted in an increase of ~50% in AUC(0-24) compared to matched
200 controls. There appeared to be no significant effect on trovafloxacin C_{max} for either group.
201 The oral clearance of trovafloxacin was reduced ~30% in both cirrhosis groups, which
202 corresponded to prolongation of half-life by 2-2.5 hours (25-30% increase) compared to

203 controls. There are no data in patients with severe cirrhosis (Child-Pugh Class C). Dosage
204 adjustment is recommended in patients with mild to moderate cirrhosis. (See **DOSAGE**
205 **AND ADMINISTRATION**)

206

207 **Renal Insufficiency**

208 The pharmacokinetics of trovafloxacin are not affected by renal impairment. Trovafloxacin
209 serum concentrations are not significantly altered in subjects with severe renal insufficiency
210 (creatinine clearance < 20 mL/min), including patients on hemodialysis.

211

212 **Photosensitivity Potential**

213 In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy
214 volunteers (12 per group), the minimum erythematous dose (MED) was measured for
215 ciprofloxacin, lomefloxacin, trovafloxacin and placebo before and after drug administration
216 for 5 days. In this study, trovafloxacin (200 mg q.d.) was shown to have a lower potential
217 for producing delayed photosensitivity skin reactions than ciprofloxacin (500 mg b.i.d.) or
218 lomefloxacin (400 mg q.d.), although greater than placebo. (See **PRECAUTIONS:**
219 **Information for Patients**)

220

221 **Drug-drug Interactions**

222 The systemic availability of trovafloxacin following oral tablet administration is significantly
223 reduced by the concomitant administration of antacids containing aluminum and magnesium
224 salts, sucralfate, vitamins or minerals containing iron, and concomitant intravenous
225 morphine administration.

226

227 Administration of trovafloxacin (300 mg p.o.) 30 minutes after administration of an
228 antacid containing magnesium hydroxide and aluminum hydroxide resulted in reductions
229 in systemic exposure to trovafloxacin (AUC) of 66% and peak serum concentration
230 (C_{max}) of 60%. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
231 **ADMINISTRATION**)

232

233 Concomitant sucralfate administration (1g) with trovafloxacin 200 mg p.o. resulted in a
234 70% decrease in trovafloxacin systemic exposure (AUC) and a 77% reduction in peak
235 serum concentration (C_{max}). (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
236 **ADMINISTRATION**)

237

238 Concomitant administration of ferrous sulfate (120 mg elemental iron) with trovafloxacin
239 200 mg p.o. resulted in a 40% reduction in trovafloxacin systemic exposure (AUC) and a
240 48% decrease in trovafloxacin C_{max}. (See **PRECAUTIONS: Drug Interactions,**
241 **DOSAGE AND ADMINISTRATION**)

242

243 Concomitant administration of intravenous morphine (0.15 mg/kg) with oral trovafloxacin
244 (200 mg) resulted in a 36% reduction in trovafloxacin AUC and a 46% decrease in
245 trovafloxacin C_{max}. Trovafloxacin administration had no effect on the
246 pharmacokinetics of morphine or its pharmacologically active metabolite, morphine-6-β-
247 glucuronide. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
248 **ADMINISTRATION**)

249

250 Minor pharmacokinetic interactions that are most likely without clinical significance include
251 calcium carbonate, omeprazole and caffeine.

252

253 Concomitant administration of calcium carbonate (1000 mg) with trovafloxacin 200 mg
254 p.o. resulted in a 20% reduction in trovafloxacin AUC and a 17% reduction in peak
255 serum trovafloxacin concentration (C_{max}).

256
257 A 40 mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg p.o.) resulted
258 in a 17% reduction in trovafloxacin AUC and a 17% reduction in trovafloxacin peak
259 serum concentration (C_{max}).

260
261 Administration of trovafloxacin (200 mg) concomitantly with caffeine (200 mg) resulted in
262 a 17% increase in caffeine AUC and a 15% increase in caffeine C_{max}. These changes
263 in caffeine exposure are not considered clinically significant.

264
265 No significant pharmacokinetic interactions include cimetidine, theophylline, digoxin, warfarin
266 and cyclosporine.

267
268 Cimetidine co-administration (400 mg twice daily for 5 days) with trovafloxacin (200 mg
269 p.o. daily for 3 days) resulted in changes in trovafloxacin AUC and C_{max} of less than
270 5%.

271
272 Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with theophylline (300 mg
273 twice daily for 14 days) resulted in no change in theophylline AUC and C_{max}.

274
275 Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with digoxin (0.25 mg
276 daily for 20 days) did not significantly alter systemic exposure (AUC) to digoxin or the
277 renal clearance of digoxin.

278
279 Trovafloxacin (200 mg p.o. daily for 7 days) does not interfere with the pharmacokinetics
280 nor the pharmacodynamics of warfarin (daily for 21 days). Concomitant oral
281 administration of trovafloxacin did not affect the systemic exposure (AUC) or peak
282 plasma concentrations (C_{max}) of the S or R isomers of warfarin, nor did it influence
283 prothrombin times.

284
285 Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with cyclosporine (daily
286 doses from 150-450 mg for 7 days) resulted in decreases of 10% or less in systemic
287 exposure to cyclosporine (AUC) and in the peak blood concentrations of cyclosporine.

288 289 Microbiology

290
291 Trovafloxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity
292 against a wide range of gram-negative and gram-positive aerobic, and anaerobic
293 microorganisms. The bactericidal action of trovafloxacin results from inhibition of DNA
294 gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the
295 replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme
296 known to play a key role in the partitioning of the chromosomal DNA during bacterial cell
297 division. Mechanism of action of fluoroquinolones including trovafloxacin is different from
298 that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines.
299 Therefore, fluoroquinolones may be active against pathogens that are resistant to these
300 antibiotics. There is no cross-resistance between trovafloxacin and the mentioned classes
301 of antibiotics. The overall results obtained from *in vitro* synergy studies, testing
302 combinations of trovafloxacin with beta-lactams and aminoglycosides, indicate that synergy
303 is strain specific and not commonly encountered. This agrees with results obtained
304 previously with other fluoroquinolones. Resistance to trovafloxacin *in vitro* develops slowly
305 via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to
306 trovafloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10} . Although
307 cross-resistance has been observed between trovafloxacin and some other
308 fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be
309 susceptible to trovafloxacin.

310
311 Trovafloxacin has been shown to be active against most strains of the following
312 microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS
313 AND USAGE section:

314
315 **Aerobic gram-positive microorganisms**
316 *Enterococcus faecalis* (many strains are only moderately susceptible)
317 *Staphylococcus aureus* (methicillin-susceptible strains)
318 *Staphylococcus epidermidis* (methicillin-susceptible strains)
319 *Streptococcus agalactiae*
320 *Streptococcus pneumoniae* (penicillin-susceptible strains)
321 *Streptococcus pyogenes*
322 Viridans group streptococci

323
324 **Aerobic gram-negative microorganisms**
325 *Escherichia coli*
326 *Gardnerella vaginalis*
327 *Haemophilus influenzae*
328 *Haemophilus parainfluenzae*
329 *Klebsiella pneumoniae*
330 *Moraxella catarrhalis*
331 *Neisseria gonorrhoeae*
332 *Proteus mirabilis*
333 *Pseudomonas aeruginosa*

334
335 **Anaerobic microorganisms**
336 *Bacteroides fragilis*
337 *Peptostreptococcus* species
338 *Prevotella* species

339
340 **Other microorganisms**
341 *Chlamydia pneumoniae*
342 *Chlamydia trachomatis*
343 *Legionella pneumophila*
344 *Mycoplasma pneumoniae*

345
346 The following *in vitro* data are available, but their clinical significance is unknown.

347
348 Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 2 $\mu\text{g/mL}$ against
349 most (90%) strains of the following microorganisms; however, the safety and effectiveness
350 of trovafloxacin in treating clinical infections due to these microorganisms have not been
351 established in adequate and well-controlled clinical trials.

352
353 **Aerobic Gram-positive microorganisms**
354 *Streptococcus pneumoniae* (penicillin-resistant strains)

355
356 **Aerobic Gram-negative microorganisms**
357 *Citrobacter freundii*
358 *Enterobacter aerogenes*
359 *Morganella morganii*
360 *Proteus vulgaris*

361
362 **Anaerobic microorganisms**

363 *Bacteroides distasonis*

364 *Bacteroides ovatus*

365 *Clostridium perfringens*

366

367 **Other microorganisms**

368 *Mycoplasma hominis*

369 *Ureaplasma urealyticum*

370

371 NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex
372 organisms are commonly resistant to trovafloxacin.

373 NOTE: The activity of trovafloxacin against *Treponema pallidum* has not been evaluated;
374 however, other quinolones are not active against *Treponema pallidum*. (See
375 WARNINGS.)

376

377 **Susceptibility Tests:**

378

379 **Dilution techniques:** Quantitative methods are used to determine antimicrobial minimum
380 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of
381 bacteria to antimicrobial compounds. The MICs should be determined using a standardized
382 procedure. Standardized procedures are based on dilution methods¹ (broth or agar) or
383 equivalent with standardized inoculum concentrations and standardized concentrations of
384 trovafloxacin mesylate powder. The MIC values should be interpreted according to the
385 following criteria:

386

387 For testing non-fastidious aerobic organisms

388

| MIC ($\mu\text{g/mL}$) | Interpretation |
|--------------------------|------------------|
| ≤ 2.0 | Susceptible (S) |
| 4.0 | Intermediate (I) |
| ≥ 8.0 | Resistant (R) |

393

394 For testing *Haemophilus* spp.^a:

395

| MIC ($\mu\text{g/mL}$) | Interpretation ^b |
|--------------------------|-----------------------------|
| ≤ 1.0 | Susceptible (S) |

398

399 ^a These interpretive standards are applicable only to broth microdilution susceptibility
400 tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)¹

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

404

405 For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^c:

406

| MIC ($\mu\text{g/mL}$) | Interpretation |
|--------------------------|------------------|
| ≤ 1.0 | Susceptible (S) |
| 2.0 | Intermediate (I) |
| ≥ 4.0 | Resistant (R) |

411

412 ^c These interpretive standards are applicable only to broth microdilution susceptibility
413 tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

414

415 For testing *Neisseria gonorrhoeae*^d:

416

417 MIC (µg/mL)

418 ≤ 0.125

419 0.25

420 ≥ 0.5

421

Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

422

423 ^d These interpretive standards are applicable to agar dilution tests with GC agar base and424 1% defined growth supplement¹.

425

426 A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the

427 antimicrobial compound in the blood reaches the concentration usually achievable. A report

428 of "Intermediate" indicates that the result should be considered equivocal, and, if the

429 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should

430 be repeated. This category implies possible clinical applicability in body sites where the

431 drug is physiologically concentrated or in situations where high dosage of drug can be used.

432 This category also provides a buffer zone which prevents small uncontrolled technical

433 factors from causing major discrepancies in interpretation. A report of "Resistant" indicates

434 that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood

435 reaches the concentration usually achievable; other therapy should be selected.

436 Standardized susceptibility test procedures require the use of laboratory control

437 microorganisms to control the technical aspects of the laboratory procedures. Standard

438 trovafloxacin mesylate powder should provide the following MIC values:

439

MicroorganismMIC Range (µg/mL)440 *Escherichia coli* ATCC 25922

0.004-0.016

441 *Staphylococcus aureus* ATCC 29213

0.008-0.03

442 *Pseudomonas aeruginosa* ATCC 27853

0.25-2.0

443 *Enterococcus faecalis* ATCC 29212

0.06-0.25

444 *Haemophilus influenzae*^e ATCC 49247

0.004-0.016

445 *Streptococcus pneumoniae*^f ATCC 49619

0.06-0.25

446 *Neisseria gonorrhoeae*^g ATCC 49226

0.004-0.016

447

448 ^e This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a449 microdilution procedure using HTM¹.450 ^f This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a

451 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed

452 horse blood.

453 ^g This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an454 agar dilution procedure using GC agar base with 1% defined growth supplement¹

455

456 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters

457 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial

458 compounds. One such standardized procedure² requires the use of standardized inoculum

459 concentrations. This procedure uses paper disks impregnated with trovafloxacin mesylate

460 equivalent to 10 µg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

461

462 Reports from the laboratory providing results of the standard single-disk susceptibility test

463 with a trovafloxacin mesylate disk (equivalent to 10 µg trovafloxacin) should be interpreted

464 according to the following criteria:

465

466

467 The following zone diameter interpretive criteria should be used for testing non-fastidious

468 aerobic organisms:

469

Zone Diameter (mm)Interpretation

| | | |
|-----|-------|------------------|
| 470 | ≥ 17 | Susceptible (S) |
| 471 | 14-16 | Intermediate (I) |
| 472 | ≤ 13 | Resistant (R) |

473

474 For testing *Haemophilus* spp.^h:

| | | |
|-----|---------------------------|-----------------------------------|
| 475 | <u>Zone Diameter (mm)</u> | <u>Interpretationⁱ</u> |
| 476 | ≥ 22 | Susceptible (S) |

477

478 ^h These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM².479 ⁱ 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.

480

481

482

483

484

484 For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^j:

485

| | | |
|-----|---------------------------|-----------------------|
| 486 | <u>Zone Diameter (mm)</u> | <u>Interpretation</u> |
| 487 | ≥ 19 | Susceptible (S) |
| 488 | 18-16 | Intermediate (I) |
| 489 | ≤ 15 | Resistant (R) |

490

491 ^j These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂

492

493

494

494 For testing *Neisseria gonorrhoeae*^k:

495

| | | |
|-----|---------------------------|-----------------------|
| 496 | <u>Zone Diameter (mm)</u> | <u>Interpretation</u> |
| 497 | ≥ 37 | Susceptible (S) |
| 498 | 34-36 | Intermediate (I) |
| 499 | ≤ 33 | Resistant (R) |

500

501 ^k These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement² incubated in 5% CO₂.

502

503

504

504 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 trovafloxacin.

505

506

507

508

509

510

511

511 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 trovafloxacin mesylate equivalent to 10-μg trovafloxacin disk should provide the following zone diameters in these laboratory quality control strains:

512

| 513 | <u>Microorganism</u> | <u>Zone Diameter Range (mm)</u> |
|-----|---|---------------------------------|
| 514 | <i>Escherichia coli</i> ATCC 25922 | 29-36 |
| 515 | <i>Staphylococcus aureus</i> ATCC 25923 | 29-35 |
| 516 | <i>Pseudomonas aeruginosa</i> ATCC 27853 | 21-27 |
| 517 | <i>Haemophilus influenzae</i> ^l ATCC 49247 | 32-39 |
| 518 | <i>Streptococcus pneumoniae</i> ^m ATCC 49619 | 25-32 |
| 519 | <i>Neisseria gonorrhoeae</i> ⁿ ATCC 49226 | 42-55 |

520

521 ^l This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM².

522

523 ^m. This quality control range is applicable only to tests performed by disk diffusion using
524 Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

525 ⁿ. This quality control range is only applicable to tests performed by disk diffusion using
526 GC agar base and 1% defined growth supplement².

527

528 **Anaerobic techniques:** For anaerobic bacteria, the susceptibility to trovafloxacin as MICs
529 can be determined by standardized test methods³. The MIC values obtained should be
530 interpreted according to the following criteria:

531

| 532 MIC ($\mu\text{g/mL}$) | 532 Interpretation |
|------------------------------|----------------------|
| 533 ≤ 2.0 | 533 Susceptible (S) |
| 534 4.0 | 534 Intermediate (I) |
| 535 ≥ 8.0 | 535 Resistant (R) |

536

537 Interpretation is identical to that stated above for results using dilution techniques.

538

539 As with other susceptibility techniques, the use of laboratory control microorganisms is
540 required to control the technical aspects of the laboratory standardized procedures.

541 Standardized trovafloxacin mesylate powder should provide the following MIC values:

542

| 543 Microorganism | 543 MIC ^p ($\mu\text{g/mL}$) |
|--|---|
| 544 <i>Bacteroides fragilis</i> ATCC 25285 | 544 0.125-0.5 |
| 545 <i>Bacteroides thetaiotaomicron</i> ATCC 29741 | 545 0.25-1.0 |
| 546 <i>Eubacterium lentum</i> ATCC 43055 | 546 0.25-1.0 |

547

548 ^p. These quality control ranges were derived from tests performed in the broth formulation
549 of Wilkins-Chalgren agar.

550

551

552 INDICATIONS AND USAGE

553

554 TROVAN is indicated for the treatment of infections caused by susceptible strains of the
555 designated microorganisms in the conditions listed below. (See **DOSAGE AND**
556 **ADMINISTRATION**)

557

558 **Nosocomial pneumonia** caused by *Escherichia coli*, *Pseudomonas aeruginosa*,
559 *Haemophilus influenzae*, or *Staphylococcus aureus*. As with other antimicrobials, where
560 *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy
561 with either an aminoglycoside or aztreonam may be clinically indicated.

562

563 **Community acquired pneumonia** caused by *Streptococcus pneumoniae*, *Haemophilus*
564 *influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*,
565 *Moraxella catarrhalis*, *Legionella pneumophila* or *Chlamydia pneumoniae*.

566

567 **Acute bacterial exacerbation of chronic bronchitis** caused by *Haemophilus influenzae*,
568 *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus*
569 *parainfluenzae*.

570

571 **Acute sinusitis** caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus*
572 *pneumoniae*.

573

574 **Complicated intra-abdominal infections, including post-surgical infections caused by**
575 *Escherichia coli*, *Bacteroides fragilis*, viridans group streptococci, *Pseudomonas aeruginosa*,
576 *Klebsiella pneumoniae*, *Peptostreptococcus* species or *Prevotella* species.

577

578 **Gynecologic and pelvic infections including endomyometritis, parametritis, septic**
579 **abortion and post-partum infections caused by** *Escherichia coli*, *Bacteroides fragilis*,
580 viridans group streptococci, *Enterococcus faecalis*, *Streptococcus agalactiae*,
581 *Peptostreptococcus* species, *Prevotella* species or *Gardnerella vaginalis*.

582

583 **Prophylaxis of infection associated with elective colorectal surgery, vaginal and**
584 **abdominal hysterectomy.**

585

586 **Uncomplicated skin and skin structure infections caused by** *Staphylococcus aureus*,
587 *Streptococcus pyogenes* or *Streptococcus agalactiae*.

588

589 **Complicated skin and skin structure infections, including diabetic foot infections,**
590 **caused by** *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*,
591 *Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. **NOTE:** TROVAN has not been
592 studied in the treatment of osteomyelitis. The safety and efficacy of TROVAN given for >4
593 weeks have not been studied. (See **PRECAUTIONS: General**)

594

595 **Uncomplicated urinary tract infections (cystitis) caused by** *Escherichia coli*.

596

597 **Chronic bacterial prostatitis caused by** *Escherichia coli*, *Enterococcus faecalis* or
598 *Staphylococcus epidermidis*.

599

600 **Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in**
601 **females caused by** *Neisseria gonorrhoeae*. (See **WARNINGS**.)

602

603 **Cervicitis due to** *Chlamydia trachomatis*. **NOTE:** In males with nongonococcal urethritis
604 TROVAN was somewhat less effective than doxycycline.

605

606 **Pelvic inflammatory disease (mild to moderate) caused by** *Neisseria gonorrhoeae* or
607 *Chlamydia trachomatis*.

608 **CONTRAINDICATIONS**

609 TROVAN is contraindicated in persons with a history of hypersensitivity to trovafloxacin,
610 alatrofloxacin, quinolone antimicrobial agents or any other components of these products.

611

612 **WARNINGS**

613 **THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC**
614 **POPULATIONS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING**
615 **WOMEN HAVE NOT BEEN ESTABLISHED.** (See **PRECAUTIONS: Pediatric Use,**
616 **Pregnancy, and Nursing Mothers** subsections.)

617

618 As with other members of the quinolone class, trovafloxacin has caused arthropathy and/or
619 chondrodysplasia in immature rats and dogs. The significance of these findings to humans
620 is unknown. (See **ANIMAL PHARMACOLOGY**.)

621

622 Convulsions, increased intracranial pressure and psychosis have been reported in patients
623 receiving quinolones. Quinolones may also cause central nervous system stimulation which
624 may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia,

625 depression, nightmares and insomnia. These reactions may occur following the first dose.
626 If these reactions occur in patients receiving trovafloxacin or alatrofloxacin, the drug should
627 be discontinued and appropriate measures instituted. (See PRECAUTIONS: General,
628 Information for Patients, Drug Interactions and ADVERSE REACTIONS.)
629

630 As with other quinolones, TROVAN should be used with caution in patients with known or
631 suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other
632 factors that predispose to seizures. (See ADVERSE REACTIONS.)
633

634 Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been
635 reported in patients receiving therapy with quinolones. These reactions may occur following
636 the first dose. Some reactions have been accompanied by cardiovascular collapse,
637 hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue,
638 laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm,
639 shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other
640 serious skin reactions.
641

642 TROVAN should be discontinued at the first appearance of a skin rash or any other sign of
643 hypersensitivity. Serious acute hypersensitivity reactions may require treatment with
644 epinephrine and other resuscitative measures, including oxygen, intravenous fluids,
645 antihistamines, corticosteroids, pressor amines and airway management, as clinically
646 indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)
647

648 Serious and sometimes fatal events, some due to hypersensitivity, and some due to
649 uncertain etiology have been reported in patients receiving therapy with all antibiotics.
650 These events may be severe and generally occur following the administration of multiple
651 doses. Clinical manifestations may include one or more of the following: fever, rash or
652 severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson
653 Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial
654 nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or
655 failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic
656 thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other
657 hematologic abnormalities.
658

659 Pseudomembranous colitis has been reported with nearly all antibacterial agents, including
660 TROVAN, and may range in severity from mild to life-threatening. Therefore, it is important
661 to consider this diagnosis in patients who present with diarrhea subsequent to the
662 administration of any antibacterial agent.
663

664 Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth
665 of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary
666 cause of "antibiotic-associated colitis."
667

668 After the diagnosis of pseudomembranous colitis has been established, therapeutic
669 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to
670 drug discontinuation alone. In moderate to severe cases, consideration should be given to
671 management with fluids and electrolytes, protein supplementation, and treatment with an
672 antibacterial drug clinically effective against *C. difficile* colitis. (See ADVERSE
673 REACTIONS.)
674

675 Although not seen in TROVAN clinical trials, ruptures of the shoulder, hand, and Achilles
676 tendons that required surgical repair or resulted in prolonged disability have been reported in
677 patients receiving quinolones. TROVAN should be discontinued if the patient experiences
678 pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise

679 until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon
680 rupture can occur during or after therapy with quinolones.

681
682 Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial
683 agents used in high doses for short periods of time to treat gonorrhea may mask or delay
684 the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test
685 for syphilis at the time of diagnosis.

686
687 **PRECAUTIONS**

688
689 **General:**
690 Because TROVAN can cause elevations of liver function tests during or soon after
691 prolonged therapy (i.e., ≥ 21 days), periodic assessment of hepatic function is advisable. The
692 safety and efficacy of TROVAN given for >4 weeks have not been studied. (See ADVERSE
693 REACTIONS)

694
695 Moderate to severe phototoxicity reactions have been observed in patients who are exposed
696 to direct sunlight while receiving some drugs in this class. Therapy should be discontinued if
697 phototoxicity (e.g., a skin eruption, etc.) occurs.

698
699 The safety and efficacy of TROVAN in patients with severe cirrhosis (Child-Pugh Class C)
700 have not been studied.

701 **Information for Patients:**

702

703 Patients should be advised:

704

705 • that TROVAN Tablets may be taken without regard to meals;

706

707 • that vitamins or minerals containing iron, aluminum-, or magnesium- base antacids,
708 antacids containing citric acid buffered with sodium citrate, or sucralfate should be taken
709 at least two hours before or two hours after taking TROVAN Tablets. (See **Drug**
710 **Interactions.**);

711

712 • that TROVAN may cause lightheadedness and/or dizziness. Dizziness and/or
713 lightheadedness was the most common adverse reaction reported, and for females
714 under 45 years, it was reported significantly more frequently than in other groups. The
715 incidence of dizziness may be substantially reduced if TROVAN Tablets are taken at
716 bedtime or with food. Patients should know how they react to trovafloxacin before they
717 operate an automobile or machinery or engage in activities requiring mental alertness
718 and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);

719

720 • to discontinue treatment and inform their physician if they experience pain, inflammation
721 or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of
722 tendinitis or tendon rupture has been confidently excluded;

723

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

729

730 • to avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds) while taking
731 TROVAN and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin
732 eruption) occurs.

733

734

735 **Drug Interactions:**

736

737 No significant interactions with theophylline, cimetidine, digoxin, warfarin or cyclosporine
738 have been observed with TROVAN Tablets (see **CLINICAL PHARMACOLOGY**).

739

740 Minor pharmacokinetic interactions without clinical significance have been observed with co-
741 administration of TROVAN Tablets with caffeine, omeprazole and calcium carbonate (see
742 **CLINICAL PHARMACOLOGY**).

743

744 Antacids, Sucralfate, and Iron: The absorption of oral trovafloxacin is significantly reduced
745 by the concomitant administration of some antacids containing magnesium or aluminum,
746 citric acid/sodium citrate (Bicitra[®]), as well as sucralfate and iron (as ferrous ions). The
747 above oral agents should be taken at least two hours before or two hours after oral
748 trovafloxacin administration (see **CLINICAL PHARMACOLOGY**).

749

750 Morphine: Co-administration of intravenous morphine significantly reduces the absorption of
751 oral trovafloxacin. Intravenous morphine should be administered at least 2 hours after oral
752 TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with

753 food. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its
754 metabolite, morphine-6- β -glucuronide. (See **CLINICAL PHARMACOLOGY**).

755
756 Alatrofloxacin should not be co-administered with any solution containing multivalent
757 cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND**
758 **ADMINISTRATION**)

759
760 **Laboratory Test Interactions:** There are no reported laboratory test interactions.

761
762 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

763
764 Long term studies in animals to determine the carcinogenic potential of trovafloxacin or
765 alatrofloxacin have not been conducted.

766
767 Trovafloxacin was not mutagenic in the Ames Salmonella reversion assay
768 or CHO/HGPRT mammalian cell gene mutation assay and it was not clastogenic in
769 mitogen-stimulated human lymphocytes or mouse bone marrow cells. A mouse
770 micronucleus test conducted with alatrofloxacin was also negative. The positive response
771 observed in the *E. coli* bacterial mutagenicity assay may be due to the inhibition of DNA
772 gyrase by trovafloxacin.

773
774 Trovafloxacin and alatrofloxacin did not affect the fertility of male or female rats at oral and
775 IV doses of 75 mg/kg/day and 50 mg/kg/day, respectively. These doses are 15 and 10
776 times the recommended maximum human dose based on mg/kg or approximately 2 times
777 based on mg/m². However, oral doses of trovafloxacin at 200 mg/kg/day (40 times the
778 recommended maximum human dose based on mg/kg or about 6 times based on mg/m²)
779 were associated with increased preimplantation loss in rats.

780
781 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**

782
783 An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg
784 maternal doses of trovafloxacin (approximately 15 times the highest recommended human
785 dose based on mg/kg or twice the based upon body surface area) were administered during
786 organogenesis. However, fetal skeletal variations were not observed in rats dosed orally with
787 15 mg/kg trovafloxacin. Evidence of fetotoxicity (increased perinatal mortality and decreased
788 body weights) was also observed in rats at 75 mg/kg. Daily oral doses of trovafloxacin at 45
789 mg/kg (approximately 9 times the highest recommended human dose based on mg/kg or
790 2.7 times based upon body surface area) in the rabbit were not associated with an increased
791 incidence of fetal skeletal variations or malformations.

792
793 An increase in skeletal variations and malformations was observed in rat fetuses after daily
794 intravenous doses of alatrofloxacin at ≥ 20 mg/kg/day (approximately 4 times the highest
795 recommended human dose based on mg/kg or 0.6 times based upon body surface area)
796 were administered to dams during organogenesis. In the rabbit, an increase in fetal skeletal
797 malformations was also observed when 20 mg/kg/day (approximately equal to the highest
798 recommended human dose based upon body surface area) of alatrofloxacin was given
799 intravenously during the period of organogenesis. Intravenous dosing of alatrofloxacin at
800 6.5 mg/kg in the rat or rabbit was not associated with an increased incidence of skeletal
801 variations or malformations. Fetotoxicity and fetal skeletal malformations have been
802 associated with other quinolones.

803
804 Oral doses of trovafloxacin >5 mg/kg were associated with an increased
805 gestation time in rats and several dams at 75 mg/kg experienced uterine dystocia.
806

807 There are no adequate and well-controlled studies in pregnant women. TROVAN should be
 808 used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
 809 (See **WARNINGS**)

810

811 Nursing Mothers:

812 Trovafloxacin is excreted in human milk and was found in measurable concentrations in the
 813 breast milk of lactating subjects (See **CLINICAL PHARMACOLOGY, Distribution**).

814

815 Because of the potential for unknown effects from trovafloxacin in nursing infants from
 816 mothers taking trovafloxacin, a decision should be made either to discontinue nursing or to
 817 discontinue the drug, taking into account the importance of the drug to the mother.

818

819 Pediatric Use:

820 The safety and effectiveness of trovafloxacin in pediatric populations less than 18 years of
 821 age have not been established. Quinolones, including trovafloxacin, cause arthropathy and
 822 osteochondrosis in juvenile animals of several species. (See **WARNINGS**)

823

824 Geriatric Use:

825 In multiple-dose clinical trials of trovafloxacin, 27% of patients were ≥ 65 years of age and
 826 12% of patients were ≥ 75 years of age. The overall incidence of drug-related adverse
 827 reactions, including central nervous system and gastrointestinal side effects, was less in the
 828 ≥ 65 year group than the other age groups.

829

830 ADVERSE REACTIONS

831 Over 6000 patients have been treated with TROVAN in multidose clinical efficacy trials
 832 worldwide.

833

834 In TROVAN studies the majority of adverse reactions were described as mild in nature (over
 835 90% were described as mild or moderate). TROVAN was discontinued for adverse events
 836 thought related to drug in 5% of patients (dizziness 2.4%, nausea 1.9%, headache 1.1%,
 837 and vomiting 1.0%).

838

839

| Trovon® Drug-Related Adverse Reactions (frequency $\geq 1\%$) in Multiple-Dose Clinical Trials | | | | |
|--|-------------------------------|-------------------------------|--|--|
| | 100 mg oral qd (N=1536) | 200 mg oral qd (N=3259) | 200 mg IV→ 200 mg oral qd (N=634) | 300 mg IV→ 200 mg oral qd (N=623) |
| Dizziness | 3% | 11% | 2% | 2% |
| Lightheadedness | 2% | 4% | 2% | <1% |
| Nausea | 4% | 8% | 5% | 4% |
| Headache | 4% | 5% | 5% | 1% |
| Vomiting | <1% | 3% | 1% | 3% |
| Diarrhea | 2% | 2% | 2% | 2% |
| Abdominal pain | <1% | 1% | 1% | 0% |
| Application/ injection/ insertion site reaction | n/a | n/a | 5% | 2% |
| Vaginitis | 1% | 1% | <1% | <1% |

| | | | | |
|----------|-----|-----|----|----|
| Pruritus | <1% | <1% | 2% | 2% |
| Rash | <1% | <1% | 2% | 2% |

840

841

Dizziness/lightheadedness on TROVAN is generally mild, lasts for a few hours following a dose, and in most cases, resolves with continued dosing. The incidence of dizziness and lightheadedness in TROVAN patients over 65 years is 3.1% and 0.6%, respectively. (See PRECAUTIONS: Information for Patients)

844

845

846

TROVAN appears to have a low potential for phototoxicity. In clinical trials with TROVAN, only mild, treatment-related phototoxicity was observed in less than 0.03% (2/7096) of patients.

847

848

849

Additional reported drug-related events in clinical trials (remotely, possibly, probably or unknown) that occurred in <1% of TROVAN-treated patients are:

850

851

852

APPLICATION/INJECTION/INCISION/INSERTION SITE:

853

Application/incision/injection/insertion site device complications, inflammation, pain, edema

854

855

AUTONOMIC NERVOUS: flushing, increased sweating, dry mouth, cold clammy skin, increased saliva

856

857

858

CARDIOVASCULAR: peripheral edema, chest pain, thrombophlebitis, hypotension, palpitation, periorbital edema, hypertension, syncope, tachycardia, angina pectoris, bradycardia, peripheral ischemia, edema, dizziness postural

859

860

861

862

CENTRAL & PERIPHERAL NERVOUS SYSTEM: confusion, paresthesia, vertigo, hypoesthesia, ataxia, convulsions, dysphonia, hypertonia, migraine, involuntary muscle contractions, speech disorder, encephalopathy, abnormal gait, hyperkinesia, hypokinesia, tongue paralysis, abnormal coordination, tremor, dyskinesia

863

864

865

866

867

GASTROINTESTINAL: abdominal pain, altered bowel habit, constipation, diarrhea-*Clostridium difficile*, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup

868

869

870

871

872

ORAL CAVITY: gingivitis, stomatitis, altered saliva, tongue disorder, tongue edema, tooth disorder, cheilitis, halitosis

873

874

875

GENERAL/OTHER: fever, fatigue, pain, asthenia, moniliasis, hot flushes, back pain, chills, infection(bacterial, fungal), malaise, sepsis, alcohol intolerance, allergic reaction, anaphylactoid reaction, drug(other) toxicity/reaction, weight increase, weight decrease

876

877

878

879

HEMATOPOIETIC: anemia, granulocytopenia, hemorrhage unspecified, leukopenia, prothrombin decreased, thrombocythemia, thrombocytopenia

880

881

882

LIVER/BILIARY: increased hepatic enzymes, hepatic function abnormal, bilirubinemia, discolored feces, jaundice

883

884

885

METABOLIC/NUTRITIONAL: hyperglycemia, thirst

886

887

MUSCULOSKELETAL: arthralgia, muscle cramps, myalgia, muscle weakness, skeletal pain, tendinitis, arthropathy

888

889

890

891 **PSYCHIATRIC:** anxiety, anorexia, agitation, nervousness, somnolence, insomnia,
892 depression, amnesia, concentration impaired, depersonalization, dreaming abnormal,
893 emotional lability, euphoria, hallucination, impotence, libido decreased-male, paroniria,
894 thinking abnormal

895
896 **REPRODUCTIVE:** Female: leukorrhea, menstrual disorder;
897 Male: balanoposthitis

898
899 **RESPIRATORY:** dyspnea, rhinitis, sinusitis, bronchospasm, coughing, epistaxis, respiratory
900 insufficiency, upper respiratory tract infection, respiratory disorder, asthma, hemoptysis,
901 hypoxia, stridor

902
903 **SKIN/APPENDAGES:** pruritus, pruritus ani, skin disorder, skin ulceration, angioedema,
904 dermatitis, dermatitis fungal, photosensitivity skin reaction, seborrhea, skin exfoliation,
905 urticaria

906
907 **SPECIAL SENSES:** taste perversion, eye pain, abnormal vision, conjunctivitis, photophobia,
908 conjunctival hemorrhage, hyperacusis, scotoma, tinnitus, visual field defect, diplopia,
909 xerophthalmia

910
911 **URINARY SYSTEM:** dysuria, face edema, micturition frequency, nephritis interstitial, renal
912 failure acute, renal function abnormal, urinary incontinence

913
914 **LABORATORY CHANGES:** Changes in laboratory parameters, without regard to drug
915 relationship, occurring in $\geq 1\%$ of TROVAN treated patients were: Decreased hemoglobin
916 and hematocrit; increased platelets; decreased and increased WBC; eosinophilia; increased
917 ALT (SGPT), AST (SGOT), and alkaline phosphatase; decreased protein and albumin;
918 increased BUN and creatinine; decreased sodium; and bicarbonate. It is not known whether
919 these abnormalities were caused by the drug or the underlying condition being treated.

920
921 The incidence and magnitude of liver function abnormalities with TROVAN were the same
922 as comparator agents except in the only study in which oral TROVAN was administered for
923 28 days. In this study (chronic bacterial prostatitis) nine percent (13/140) of TROVAN-treated
924 patients experienced elevations of serum transaminases (AST and/or ALT) of ≥ 3 times the upper
925 limit of normal. These liver function test abnormalities generally developed at the end of, or following
926 completion of, the planned 28-day course of therapy, but were not associated with concurrent
927 elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline
928 phosphatase, or lactate dehydrogenase). Patients were asymptomatic with these abnormalities,
929 which generally returned to normal within 1-2 months after discontinuation of therapy. (See
930 **PRECAUTIONS - General**)

931
932 **OVERDOSAGE**

933
934 Trovafloxacin has a low order of acute toxicity. The minimum lethal oral dose in mice and
935 rats was 2000 mg/kg or greater. The minimum lethal i.v. dose for the prodrug, alatrofloxacin,
936 was 50-125 mg/kg for mice and greater than 75 mg/kg for rats. Clinical signs observed
937 included decreased activity and respiration, ataxia, ptosis, tremors and convulsions.

938
939 In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting
940 or by gastric lavage. The patient should be carefully observed and given symptomatic and
941 supportive treatment. Adequate hydration should be maintained. Trovafloxacin is not
942 efficiently removed from the body by hemodialysis.

943
944

968
969

| DOSAGE GUIDELINES | | |
|--|--|--|
| INFECTION* / LOCATION AND TYPE | DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION | TOTAL DURATION |
| Nosocomial Pneumonia (See NOTE 1 below.) | 300 mg I.V. followed by 200 mg oral | 10-14 days |
| Community Acquired Pneumonia | 200 mg oral or 200 mg I.V. followed by 200 mg oral | 7-14 days |
| Acute Bacterial Exacerbation of Chronic Bronchitis | 100 mg oral | 7-10 days |
| Acute Sinusitis | 200 mg oral | 10 days |
| Complicated Intra-Abdominal Infections, including post-surgical infections | 300 mg I.V. followed by 200 mg oral | 7-14 days |
| Gynecologic and Pelvic Infections | 300 mg I.V. followed by 200 mg oral | 7-14 days |
| Surgical Prophylaxis - Elective Colorectal Surgery (See NOTE 2 below.) | 200 mg I.V. or oral | Single intravenous or oral dose within 30 min. to 4 hours before surgery |
| Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy (See NOTE 2 below.) | 200 mg I.V. or oral | Single intravenous or oral dose within 30 min. to 4 hours before surgery |
| Skin and Skin Structure Infections, Uncomplicated | 100 mg Oral | 7-10 days |
| Skin and Skin Structure Infections, Complicated, including diabetic foot infections | 200 mg oral or 200 mg I.V. followed by 200 mg oral | 10-14 days |
| Uncomplicated Urinary Tract Infections (cystitis) | 100 mg oral | 3 days |
| Chronic Bacterial Prostatitis | 200 mg oral | 28 days |
| Uncomplicated Urethral Gonorrhea Males; Endocervical and Rectal Gonorrhea in Females | 100 mg oral | Single Dose |
| Cervicitis due to <i>Chlamydia trachomatis</i> | 200 mg oral | 5 days |
| Pelvic Inflammatory Disease (mild to moderate) | 200 mg oral | 14 days |

* due to the designated pathogens (See INDICATIONS AND USAGE)

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NOTE 1: As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

NOTE 2: In patients where surgical prophylaxis with oral TROVAN is indicated, Bicitra® should not be given within 2 hours. (See PRECAUTIONS: Drug Interactions)

The safety and efficacy of TROVAN use for >4 weeks have not been studied. (See PRECAUTIONS.)

IMPAIRED RENAL FUNCTION: No adjustment in the dosage of TROVAN is necessary in patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.

987 **CHRONIC HEPATIC DISEASE (cirrhosis):** The following table provides dosing guidelines
988 for patients with mild or moderate cirrhosis (Child-Pugh Class A and B). There are no data in
989 patients with severe cirrhosis (Child-Pugh Class C).
990

| INDICATED DOSE (Normal hepatic function) | CHRONIC HEPATIC DISEASE DOSE |
|--|------------------------------|
| 300 mg i.v. | 200 mg i.v. |
| 200 mg i.v. or oral | 100 mg i.v. or oral. |
| 100 mg oral | 100 mg oral |

991

992 INTRAVENOUS ADMINISTRATION

993 AFTER DILUTION WITH AN APPROPRIATE DILUENT TROVAN I.V. SHOULD BE
994 ADMINISTERED BY INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES.
995 CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.

996 TROVAN I.V. is supplied in single-use vials containing a concentrated solution of
 997 alatrofloxacin mesylate in Water for Injection (equivalent of 200 mg or 300 mg as
 998 trovafloxacin). Each mL contains alatrofloxacin mesylate equivalent to 5 mg trovafloxacin.
 999 (See **HOW SUPPLIED** for container sizes.) **THESE TROVAN I.V. SINGLE-USE VIALS**
 1000 **MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO**
 1001 **INTRAVENOUS ADMINISTRATION.** This parenteral drug product should be inspected
 1002 visually for discoloration and particulate matter prior to dilution and administration. Since no
 1003 preservative or bacteriostatic agent is present in this product, aseptic technique must be
 1004 used in preparation of the final parenteral solution.

1005
 1006 **PREPARATION OF ALATROFLOXACIN MESYLATE INJECTION FOR ADMINISTRATION**

1007 The intravenous dose should be prepared by aseptically withdrawing the appropriate
 1008 volume of concentrate from the vials of TROVAN I.V. This should be diluted with a suitable
 1009 intravenous solution to a final concentration of 1-2 mg/mL. (See **Compatible Intravenous**
 1010 **Solutions.**) The resulting solution should be infused over a period of
 1011 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already
 1012 be in place.

1013
 1014 Since the vials are for single-use only, any unused portion should be discarded.

1015
 1016 Since only limited data are available on the compatibility of alatrofloxacin intravenous
 1017 injection with other intravenous substances, additives or other medications should not be
 1018 added to TROVAN I.V. in single-use vials or infused simultaneously through the same
 1019 intravenous line.

1020
 1021 If the same intravenous line is used for sequential infusion of several different drugs, the line
 1022 should be flushed before and after infusion of TROVAN I.V. with an infusion solution
 1023 compatible with TROVAN I.V. and with any other drug(s) administered via this common line.

1024
 1025 If TROVAN I.V. is to be given concomitantly with another drug, each drug should be given
 1026 separately in accordance with the recommended dosage and route of administration for
 1027 each drug.

1028
 1029 The desired dosage of TROVAN I.V. may be prepared according to the following chart:
 1030

| DOSAGE STRENGTH (mg) (trovafloxacin equivalent) | VOLUME TO WITHDRAW (mL) | DILUENT VOLUME (mL) | TOTAL VOLUME (mL) | INFUSION CONC (mg/mL) |
|--|----------------------------|------------------------|-------------------------|--------------------------|
| 100 mg | 20 | 30 | 50 | 2 |
| 100 mg | 20 | 80 | 100 | 1 |
| 200 mg | 40 | 60 | 100 | 2 |
| 200 mg | 40 | 160 | 200 | 1 |
| 300 mg | 60 | 90 | 150 | 2 |
| 300 mg | 60 | 240 | 300 | 1 |

1031
 1032 For example, to prepare a 200 mg dose at an infusion concentration of 2 mg/mL (as
 1033 trovafloxacin), 40 mL of TROVAN I.V. is withdrawn from a vial and diluted with 60 mL of a
 1034 compatible intravenous fluid to produce a total infusion solution volume of 100 mL.

1035
 1036 **Compatible Intravenous Solutions:**

1037 5% Dextrose Injection, USP
 1038 0.45% Sodium Chloride Injection, USP
 1039 5% Dextrose and 0.45% Sodium Chloride Injection, USP
 1040 5% Dextrose and 0.2% Sodium Chloride Injection, USP
 1041 Lactated Ringer's and 5% Dextrose Injection, USP

1042 Stability of TROVAN I.V. as supplied:
1043 When stored under recommended conditions, TROVAN I.V., as supplied in (20-mL) 40 mL
1044 or 60 mL vials, is stable through the expiration date printed on the label.

1045

1046 **Stability of TROVAN I.V. Following Dilution:**

1047 TROVAN I.V., when diluted with the following intravenous solutions to concentrations of
1048 0.5 to 2.0 mg/mL (as trovafloxacin), is physically and chemically stable for up to 7 days
1049 when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic
1050 (PVC type) intravenous containers.

1051

1052 **HOW SUPPLIED**

1053 **Tablets**

1054 TROVAN (trovafloxacin mesylate) Tablets are available as blue, film-coated tablets. The
1055 100 mg tablets are round and contain trovafloxacin mesylate equivalent to 100 mg
1056 trovafloxacin. The 200 mg tablets are modified oval-shaped and contain trovafloxacin
1057 mesylate equivalent to 200 mg trovafloxacin.

1058

1059 TROVAN Tablets are packaged and in unit dose blister strips in the following configurations:

1060

1061 100-mg tablets: color: blue; shape: round

1062 debossing: "PFIZER" on side 1 and "378" on side 2

1063 Bottles of 30 (NDC 0049-3780-30)

1064 Unit Dose/ 40 tablets (NDC 0049-3780-43)

1065

1066 200-mg tablets: color: blue; shape: modified oval

1067 debossing: "PFIZER" on side 1 and "379" on side 2

1068 Bottles of 30 (NDC 0049-3790-30)

1069 Unit Dose/ 40 tablets (NDC 0049-3790-43)

1070

1071 **Storage**

1072 TROVAN Tablets should be stored at 15 °C to 30 °C (59 °F to 86 °F) in well-closed
1073 containers.

1074

1075 **Injection**

1076 TROVAN is also available for intravenous administration as the prodrug, TROVAN I.V.
1077 (alatrofloxacin mesylate injection), in the following configurations:

1078 Single-use vials containing a clear, colorless to pale-yellow concentrated solution of
1079 alatrofloxacin mesylate equivalent to 5 mg trovafloxacin/mL.

1080

1081 5 mg/mL, 40 mL, 200 mg

1082 Unit dose package (NDC 0049-3890-28)

1083

1084 5 mg/mL, 60 mL, 300 mg

1085 Unit dose package (NDC 0049-3900-28)

1086

1087 **Storage**

1088 TROVAN I.V. should be stored at 15 °C to 30 °C (59 °F to 86 °F). Protect From Light. Do
1089 Not Freeze.

1090

1091 **ANIMAL PHARMACOLOGY:**

1092

1093 Quinolones have been shown to cause arthropathy in immature animals.

1094

1095 Arthropathy and chondrodysplasia were observed in immature animals given trovafloxacin
 1096 (See **WARNINGS**).
 1097
 1098 At doses from 10 to 15 times the human dose based on a mg/kg or approximately 3 to
 1099 5 times based on mg/m², trovafloxacin has been shown to cause arthropathy in immature
 1100 rats and dogs. In addition, these drugs are associated with an increased incidence of
 1101 chondrodysplasia in rats compared to controls. There is no evidence of arthropathies in fully
 1102 mature rats and dogs at doses from 40 or 10 times the human dose based on mg/kg or
 1103 approximately 5 times based on mg/m² for a 6 month exposure period.
 1104
 1105 Unlike some other members of the quinolone class, crystalluria and ocular toxicity were not
 1106 observed in chronic safety studies with rats or dogs with either trovafloxacin or its prodrug,
 1107 alatrofloxacin.
 1108
 1109 Quinolones have been reported to have proconvulsant activity that is exacerbated with
 1110 concomitant use of non-steroidal antiinflammatory drugs (NSAIDs). Neither trovafloxacin
 1111 administered orally at 500 mg/kg, nor alatrofloxacin administered intravenously at 75 mg/kg,
 1112 showed an increase in measures of seizure activity in mice at doses when used in
 1113 combination with the active metabolite of the NSAID, fenbufen.
 1114
 1115 As with other members of the quinolone class, trovafloxacin at doses 5 to 10 times the
 1116 human dose based on mg/kg or 1 to 5 times the human dose based on mg/m² produces
 1117 testicular degeneration in rats and dogs dosed for 6 months.
 1118
 1119 At a dose of trovafloxacin 10 times the highest human dose based on mg/kg or
 1120 approximately 5 times based on mg/m², elevated liver enzyme levels which correlated with
 1121 centrilobar hepatocellular vacuolar degeneration and necrosis were observed in dogs in a
 1122 6 month study. A subsequent study demonstrated reversibility of these effects when
 1123 trovafloxacin was discontinued.

1124 CLINICAL STUDIES

1125 Acute Bacterial Exacerbation of Chronic Bronchitis

1126 Patients with clinically documented acute bacterial exacerbation of chronic bronchitis
 1127 participated in a randomized, double blind, multicenter trial comparing oral trovafloxacin
 1128 (100mg once daily) with oral clarithromycin (500mg twice daily) for 7 days. The clinical
 1129 success rate (cure + improvement, with no need for further antibiotic therapy) at the End of
 1130 Treatment was 89% (181/203) and 85% (160/188) for trovafloxacin and clarithromycin
 1131 respectively. The clinical success rate at the End of Study (Day 28) was 80% (158/197) and
 1132 74% (134/178) for trovafloxacin and clarithromycin respectively.
 1133
 1134

1135 The following are the clinical success rates for the clinically evaluable groups by pathogen:
 1136
 1137

| Pathogen | End of Treatment | | End of Study | |
|--------------------------|-------------------------|------------------------------|-------------------------|------------------------------|
| | Trovafloxacin 100 mg | Clarithromycin 500 mg BID | Trovafloxacin 100 mg | Clarithromycin 500 mg BID |
| <i>H. influenzae</i> | 92% (24/26) | 89% (16/18) | 92% (24/26) | 44% (7/16)* |
| <i>M. catarrhalis</i> | 78% (14/18) | 80% (16/20) | 71% (12/17) | 74% (14/19) |
| <i>S. pneumoniae</i> | 100% (7/7) | 91% (10/11) | 86% (6/7) | 91% (10/11) |
| <i>H. parainfluenzae</i> | 100% (6/6) | 86% (6/7) | 100% (6/6) | 86% (6/7) |
| <i>S. aureus</i> | 93% (13/14) | 83% (10/12) | 85% (11/13) | 75% (9/12) |

1138 *p= 0.001

1139

1140 Of the above patients with clinical failure at end of treatment or study, no trovafloxacin and 2
 1141 clarithromycin patients (both *H. influenzae*) had positive post treatment cultures for the
 1142 baseline pathogen. There was no emergence of resistance in either treatment group.
 1143 Fewer patients required hospitalization during study (Day 1-35) in the trovafloxacin group
 1144 (3/210) than in the clarithromycin group (10/200), p=0.039.

1145

1146 **Hospitalized Community Acquired Pneumonia**

1147 Adult patients with clinically and radiologically documented community acquired pneumonia,
 1148 requiring hospitalization and initial intravenous therapy, participated in two randomized,
 1149 multicenter, double-blind, double-dummy trials. The first trial compared intravenous
 1150 alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once
 1151 daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) plus
 1152 ampicillin (500mg QID) for 2 to 7 days followed by oral ciprofloxacin (500mg BID) plus
 1153 amoxicillin (500mg TID) for a total of 7 to 14 days of therapy. The second study compared
 1154 intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin
 1155 (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ceftriaxone (1000mg
 1156 once daily for 2 to 7 days) followed by oral cefpodoxime (400mg BID) for 7 to 14 days of
 1157 total therapy with optional blinded erythromycin added to the ceftriaxone/cefpodoxime arm if
 1158 an atypical pneumonia was suspected.

1159

1160 The clinical success rate (cure + improvement with no need for further antibiotic therapy) at
 1161 the End of Treatment was 90% (311/346) and 90% (325/363) for TROVAN and the
 1162 comparator agents respectively. The clinical success rate at the End of Study (Day 30) was
 1163 86% (256/299) and 85% (283/334) for TROVAN and the comparator agents respectively.
 1164 All cause mortality (Day 1-35) was 2.45% (10/408) on TROVAN and 5.45% (23/422) on the
 1165 comparator agents.

1166

1167 The following outcomes are the clinical success rates for the clinically evaluable patient
 1168 groups by pathogen in these two studies:

1169

| Pathogen | End of Treatment | | End of Study | |
|-----------------------|------------------|--------------|--------------|-------------|
| | TROVAN | Comparators | TROVAN | Comparators |
| <i>S. pneumoniae</i> | 89% (63/71) | 95% (62/65) | 87% (55/63) | 91% (50/55) |
| <i>H. influenzae</i> | 97% (35/36) | 94% (46/49) | 90% (28/31) | 94% (44/47) |
| <i>M. catarrhalis</i> | 100% (8/8) | 100% (4/4) | 100% (6/6) | 100% (4/4) |
| <i>S. aureus</i> | 100% (8/8) | 93% (13/14) | 100% (6/6) | 91% (10/11) |
| <i>K. pneumoniae</i> | 100% (3/3) | 89% (8/9) | 100% (3/3) | 86% (6/7) |
| <i>L. pneumophila</i> | 77% (10/13) | 86% (12/14) | 75% (9/12) | 86% (12/14) |
| <i>M. pneumoniae</i> | 100% (20/20) | 87% (13/15) | 94% (17/18) | 79% (11/14) |
| <i>C. pneumoniae</i> | 75% (6/8) | 100% (18/18) | 67% (4/6) | 94% (16/17) |

1170

1171 Of the above patients with clinical failure at end of treatment or study, only one alatrofloxacin
 1172 patient (*H. influenzae* + *S. pneumoniae*) and one ceftriaxone + erythromycin patient
 1173 (*Legionella*) had a microbiologically confirmed persistent pathogen at the time of failure with
 1174 no emergence of resistance in either study.

1175

1176 **Nosocomial Pneumonia**

1177 Adult patients with clinically and radiologically documented nosocomial pneumonia,
 1178 participated in a randomized, multicenter, double-blind, double-dummy trial comparing
 1179 intravenous alatrofloxacin (300mg once daily for 2 to 7 days) followed by oral trovafloxacin
 1180 (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg
 1181 BID) for 2 to 7 days followed by oral ciprofloxacin (750mg BID) for a total of 7 to 14 days of
 1182 therapy with optional blinded clindamycin or metronidazole added to the ciprofloxacin arm if
 1183 an anaerobic pneumonia was suspected. In subjects with documented *Pseudomonas*
 1184 infection or methicillin-resistant *S. aureus*, aztreonam or vancomycin, respectively, could
 1185 have been added to either treatment regimen.

1186
 1187 The clinical success rate (cure + improvement with no need for further antibiotic therapy) at
 1188 the End of Treatment was 77% (68/88) and 78% (79/101) for TROVAN and ciprofloxacin
 1189 respectively. The clinical success rate at the End of Study (Day 30) was 69% (50/72) and
 1190 68% (54/79) for TROVAN and ciprofloxacin respectively.

1191
 1192 The following outcomes are the clinical success rates for the clinically evaluable patient
 1193 groups by pathogen:
 1194

| Pathogen | End of Treatment | | End of Study | |
|----------------------|------------------|---------------|--------------|---------------|
| | TROVAN | Ciprofloxacin | TROVAN | Ciprofloxacin |
| <i>P. aeruginosa</i> | 67% (10/15) | 55% (6/11) | 62% (8/13) | 25% (2/8) |
| <i>H. influenzae</i> | 88% (7/8) | 89% (8/9) | 83% (5/6) | 86% (6/7) |
| <i>E. coli</i> | 71% (5/7) | 80% (4/5) | 50% (3/6) | 80% (4/5) |
| <i>S. aureus</i> | 64% (7/11) | 80% (8/10) | 50% (4/8) | 67% (4/6) |

1195
 1196 Of the above patients with clinical failure at end of treatment or study, two alatrofloxacin
 1197 patients (*S.aureus*, *P.aeruginosa*) and 4 ciprofloxacin patients (all *P.aeruginosa*) had a
 1198 microbiologically confirmed persistent pathogen at the time of failure. Three of the 4
 1199 ciprofloxacin patients with clinical failure and persistence had emergence of resistance with
 1200 none on alatrofloxacin.

1201

1202 **Complicated Intra-Abdominal Infections**

1203 Patients hospitalized with clinically-documented, complicated intra-abdominal infections,
 1204 including post-surgical infections participated in a randomized, double-blind, multicenter trial
 1205 comparing intravenous alatrofloxacin (300 mg once daily) followed by oral trovafloxacin (200
 1206 mg once daily) to intravenous imipenem/cilastatin (1g q8h) followed by oral
 1207 amoxicillin/clavulanic acid (500 mg TID) for a maximum of 14 days of therapy. The clinical
 1208 success rate (cure + improvement) at the End of Treatment was 88% (136/155) and 86%
 1209 (122/142) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic
 1210 acid, respectively. The clinical success rate at the End of Study (Day 30) was 83%
 1211 (129/156) and 84% (127/152) for alatrofloxacin→trovafloxacin and
 1212 imipenem/cilastatin→amoxicillin/clavulanic acid respectively.

1213

1214 The following are the clinical success rates for the clinically-evaluable patient groups by
 1215 pathogen:
 1216

| Pathogen | End of Treatment | | End of Study | |
|----------------|------------------|----------------------------|--------------|----------------------------|
| | TROVAN | Imipenem/Cila Amox/Clav | TROVAN | Imipenem/Cila Amox/Clav |
| <i>E. coli</i> | 94% (72/77) | 90% (52/58) | 86% (66/77) | 86% (51/59) |

| | | | | |
|--------------------------------|-------------|-------------|-------------|-------------|
| <i>Bacteroides fragilis</i> | 97% (30/31) | 82% (28/34) | 84% (26/31) | 75% (27/36) |
| viridans group streptococci | 90% (18/20) | 83% (19/23) | 90% (18/20) | 78% (18/23) |
| <i>Pseudomonas aeruginosa</i> | 94% (15/16) | 82% (14/17) | 88% (14/16) | 83% (15/18) |
| <i>Klebsiella pneumoniae</i> | 80% (12/15) | 71% (10/14) | 67% (10/15) | 71% (10/14) |
| <i>Peptostreptococcus</i> spp. | 86% (12/14) | 88% (7/8) | 79% (11/14) | 75% (6/8) |
| <i>Prevotella</i> spp. | 77% (10/13) | 50% (2/4) | 77% (10/13) | 60% (3/5) |

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Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

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