CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-537/S-068

Trade Name: Cipro

Generic Name: ciprofloxacin hydrochloride

Sponsor: Bayer Healthcare

Approval Date: 10/03/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	
Labeling	✓
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	✓
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-068
NDA 19-847/S-042
NDA 19-857/S-049
NDA 20-780/S-026
NDA 21-473/S-024

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Dr. Herrington:

Please refer to your supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Drug Product Name	**NDA Number**	**Supplement number**	**Date of supplement**	**Date of receipt**
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-068	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-042	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-049	August 5, 2008	August 6, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-026	August 5, 2008	August 6, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-024	August 5, 2008	August 6, 2008

We acknowledge receipt of your submissions dated September 5, September 25, and October 2, 2008.

Reference is also made to the FDA letter dated July 7, 2008 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for fluoroquinolone antimicrobial drugs. This information pertained to the risk of tendon-related adverse events with the use of fluoroquinolones.

Your supplemental new drug applications provide for revisions to the labeling for all CIPRO (ciprofloxacin) products, consistent with our July 7, 2008 letter and August 25, September 17, and October 2, 2008 correspondences.

These supplemental new drug applications provide for the following changes to product labeling (additions are noted by underline and deletions are noted by ~~strikethrough~~ replacing "CIPRO" with "CIPRO XR" where appropriate in the Cipro XR labeling):

1. A **Boxed Warning** with bolded font and enclosed in a black box was added to the beginning of the labeling as follows:

> **WARNING:**
> **Fluoroquinolones, including CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).**

2. The **WARNINGS/Tendon Effects** subsection of the labeling was renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** section, and updated as follows:

Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

~~**Tendon Effects:** Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Ciprofloxacin 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 tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.~~

3. The information on tendon adverse reactions in the **PRECAUTIONS/ Information for Patients** subsection of the labeling was moved to the first bullet of the subsection and updated as follows:

   - to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
   - ~~to discontinue CIPRO treatment, rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids.~~

4. The information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling was moved to the first paragraph of the subsection and updated as follows:

   Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve~~s~~ the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

   ~~Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.~~

5. The Patient Package Insert for CIPRO Tablets, Oral Suspension, I.V., and CIPRO XR was replaced with a Medication Guide, and the complete Medication Guide is located at the end of the Package Insert.

We have completed our review of these supplemental applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "**SPL for approved supplements NDA 19-537/S-068, NDA 19-847/S-042, NDA 19-857/S-049, NDA 20-780/S-026, and NDA 21-473/S-024".**

In addition, within 21 days of the date of this letter, amend any pending applications for these NDAs with content of labeling in structured product labeling (SPL) format to include the changes approved in these applications.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter and that the revised labeling be reflected in the next printing of the labeling. While you may use labeling already printed as of the date of this letter until January 3, 2009, after that date we request that the revised labeling accompany any newly shipped product.

Failure to make these changes promptly could make your product misbranded under Sections 201(n) and 502(a) of FDCA.

Please note that you must comply with the Medication Guide Regulations as specified in 21 CFR 208. In particular, the carton and container labels must comply with 21 CFR208.24 (a)(2)(d). Please submit proposed labels for review within 30 days of receipt of this letter.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure (Final Product Labeling, including Medication Guide)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

10/3/2008 08:00:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

LABELING

CIPRO®
(ciprofloxacin hydrochloride)
TABLETS

CIPRO®
(ciprofloxacin*)
ORAL SUSPENSION

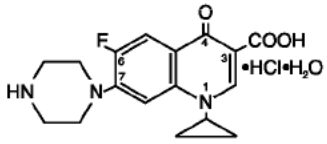
WARNING:
Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

08935877, R.5 1/08

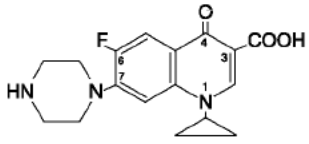
To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO® Tablets and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral Suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:



Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ 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 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, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol.

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 regard 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 (µg/mL)	Area Under Curve (AUC) (µg•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 µg/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 (µg•hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max} (µg/mL)	2.97	4.56	3.59	4.07

[a] AUC_{0-12h}
[b] $AUC\ 24h = AUC_{0-12h} \times 2$
[c] $AUC\ 24h = AUC_{0-8h} \times 3$

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, skin, 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. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug (see **CONTRAINDICATIONS**; **WARNINGS**; **PRECAUTIONS: Drug Interactions**).

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 µg/mL during the first two hours and are approximately 30 µg/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 with tizanidine is contraindicated **(**See **CONTRAINDICATIONS)**. 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 **WARNINGS: 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 preliminary 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.

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 µg/mL (range: 1.5 – 3.4 µg/mL) and the mean AUC was 9.2 µg*h/mL (range: 5.8 – 14.9 µg*h/mL). There was no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg TID).

In children with severe sepsis who were given intravenous ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 µg/mL (range: 4.6 – 8.3 µg/mL) in 10 children less than 1 year of age; and 7.2 µg/mL (range: 4.7 – 11.8 µg/mL) in 10 children between 1 and 5 years of age. The AUC values were 17.4 µg*h/mL (range: 11.8 – 32.0 µg*h/mL) and 16.5 µg*h/mL (range: 11.0 – 23.8 µg*h/mL) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4 - 5 hours, and the bioavailability of the oral suspension is approximately 60%.

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 vitro* 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	*Proteus mirabilis*
Citrobacter diversus	*Proteus vulgaris*
Citrobacter freundii	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Escherichia coli	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Salmonella typhi*
Haemophilus parainfluenzae	*Serratia marcescens*
Klebsiella pneumoniae	*Shigella boydii*
Moraxella catarrhalis	*Shigella dysenteriae*
Morganella morganii	*Shigella flexneri*
Neisseria gonorrhoeae	*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 µg/mL or less against most (≥ 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 Iwoffi	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	*Vibrio cholerae*
Enterobacter aerogenes	*Vibrio parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella pneumophila	*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 method[1] (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 *Enterobacteriaceae, Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* [a]:

MIC (µg/mL)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

[a]These 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*[b]*:*

MIC (µg/mL)	Interpretation
≤1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].
The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.
For testing *Neisseria gonorrhoeae*[c]*:*

MIC (µg/mL)	Interpretation
≤ 0.06	Susceptible (S)
0.12 – 0.5	Intermediate (I)
≥1	Resistant (R)

[c] This 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 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		MIC (µg/mL)
E. faecalis	ATCC 29212	0.25 – 2.0
E. coli	ATCC 25922	0.004 – 0.015
H. influenzae[a]	ATCC 49247	0.004 – 0.03
N. gonorrhoeae[b]	ATCC 49226	0.001 – 0.008
P. aeruginosa	ATCC 27853	0.25 – 1.0
S. aureus	ATCC 29213	0.12 – 0.5

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

[b]This 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.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] 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 *Enterobacteriaceae, Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* [a]:

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

[a]These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]*:*

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

[b]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*[c]:

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

[c]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		Zone Diameter (mm)
E. coli	ATCC 25922	30 – 40
H. influenzae[a]	ATCC 49247	34 – 42
N. gonorrhoeae[b]	ATCC 49226	48 – 58
P. aeruginosa	ATCC 27853	25 – 33
S. aureus	ATCC 25923	22 – 30

[a] These quality control limits are applicable to only *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 and patient populations listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Adult Patients:

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

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

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 penicillin-susceptible *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,* penicillin-susceptible *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,* methicillin-susceptible *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.*

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii* †**,** *Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei*† 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.*

Pediatric patients (1 to 17 years of age):

Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli.*

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

Adult and Pediatric Patients:

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

Ciprofloxacin serum concentrations achieved in humans served as a surrogate endpoint reasonably likely to predict clinical benefit and provided the initial basis for approval of this indication.[4] Supportive clinical information for ciprofloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001. (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

†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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO Tablets and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral Suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS**: **Drug Interactions**.)

WARNINGS

Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Pregnant Women: THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pregnancy,** and **Nursing Mothers** subsections.)

Pediatrics: Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS**.)

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

Cytochrome P450 (CYP450): Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g. theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug.

Central Nervous System Disorders: 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**.)

Theophylline: 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.

Hypersensitivity Reactions: 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.

Other 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 ciprofloxacin. 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, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

Pseudomembranous Colitis: *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be

instituted as clinically indicated.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

Syphilis: 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.

Central Nervous System: 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**.)

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

Photosensitivity/Phototoxicity: Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (See **ADVERSE REACTIONS and ADVERSE REACTIONS/ Post-Marketing Adverse Events).**

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

Prescribing CIPRO Tablets and CIPRO Oral Suspension in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients:

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs,

and in patients with kidney, heart or lung transplants.

- that antibacterial drugs including CIPRO Tablets and CIPRO Oral Suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO Tablets and CIPRO Oral Suspension is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO Tablets and CIPRO Oral Suspension or other antibacterial drugs in the future.
- 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, Videx® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, 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.
- that photosensitivity/phototoxicity has been reported in patients receiving quinolone antibiotics. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.
- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- 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 increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- 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.
- that ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See **WARNINGS, PRECAUTIONS, Pediatric Use** and **ADVERSE REACTIONS**.)
- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as

two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions: In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (Cmax 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

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, Videx® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, 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 H_2-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 sulfonylurea 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 significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

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 V_{79} 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
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon mg/m^2).

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/m^2), 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.[3]

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 (approximately 0.7-times the highest recommended therapeutic dose based upon mg/m^2) 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 TERIS – 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.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] 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 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] 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.[7,8] 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, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic dose based upon mg/m^2) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced 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: Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL PHARMACOLOGY**.)

Inhalational Anthrax (Post-Exposure)
Ciprofloxacin is indicated in pediatric patients for 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**.

Complicated Urinary Tract Infection and Pyelonephritis
Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*. Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including events related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within six weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Cystic Fibrosis
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 I.V. 10 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 I.V. 50 mg/kg/dose q8h and tobramycin I.V. 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.
Musculoskeletal adverse events in patients with cystic fibrosis 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. Other adverse events were similar in nature and frequency between treatment arms. 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 can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.
Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

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**.)

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Adverse Reactions in Adult Patients: 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, 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, hypotension

CENTRAL NERVOUS SYSTEM: restlessness, dizziness, lightheadedness, 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

HEMIC/LYMPHATIC: lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism

SKIN/HYPERSENSITIVITY: allergic reaction, pruritus, urticaria, photosensitivity/ phototoxicity reaction, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae 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 - 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Adverse Reactions in Pediatric Patients: Ciprofloxacin, administered I.V. and /or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or

pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received I.V. or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC

	Ciprofloxacin	**Comparator**
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval*	(-0.8%, +7.2%)	
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, + 9.1%)	

*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence

interval indicated that it could not be concluded that ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or post-marketing experience may also occur in pediatric patients.

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 (including life-threatening anaphylactic shock), anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), photosensitivity/phototoxicity reaction, 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, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

Adverse events were also reported by persons who received ciprofloxacin for anthrax post-exposure prophylaxis following the anthrax bioterror attacks of October 2001. (See also **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**.)

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 gammaglutamyl 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, aluminum, 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 hypoactivity 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 - ADULTS

CIPRO Tablets and Oral Suspension should be administered orally to adults 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, Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, other highly buffered drugs, or other products containing calcium, iron or zinc.

ADULT DOSAGE GUIDELINES

Infection	Severity	Dose	Frequency	Usual Durations†
Urinary Tract	Acute Uncomplicated	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)**		500 mg	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.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Conversion of I.V. to Oral Dosing in Adults: 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

Cipro Oral Dosage	Equivalent Cipro 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

Adults with 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:

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. Patients should be carefully monitored.

DOSAGE AND ADMINISTRATION - PEDIATRICS

CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Dosing and initial route of therapy (i.e., I.V. or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6 to 10 mg/kg I.V. every 8 hours and allowed to switch to oral therapy (10 to 20 mg/kg every 12 hours), at the discretion of the physician.

PEDIATRIC DOSAGE GUIDELINES				
Infection	Route of Administration	Dose (mg/kg)	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)	Intravenous	6 to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 8 hours	10-21 days*
	Oral	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 12 hours	
Inhalational Anthrax (Post-Exposure)**	Intravenous	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
	Oral	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	

* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).

** Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (i.e., creatinine clearance of < 50 mL/min/1.73m^2).

HOW SUPPLIED

CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 250 mg ciprofloxacin. The 250 mg tablet is coded with the word "BAYER" on one side and "CIP 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 "BAYER" on one side and "CIP 500" on the reverse side. The 750 mg tablet is coded with the word "BAYER" on one side and "CIP 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.

	Strength	NDC Code	Tablet Identification
Bottles of 50:	750 mg	NDC 0085-1756-01	CIPRO 750
Bottles of 100:	250 mg	NDC 0085-1758-01	CIPRO 250
	500 mg	NDC 0085-1754-01	CIPRO 500
Unit Dose			
Package of 100:	250 mg	NDC 0085-1758-02	CIPRO 250
	500 mg	NDC 0085-1754-02	CIPRO 500
	750 mg	NDC 0085-1756-02	CIPRO 750

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	0085-1777-01
10%	100 mL	500 mg/5 mL	10,000 mg	0085-1773-01

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 young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3- and 3.5-times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, 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, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single oral doses as low as 5 mg/kg. (approximately 0.07-times the highest recommended therapeutic dose based upon mg/m^2). 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 (approximately 0.2-times the highest recommended therapeutic dose based upon mg/m^2).

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 pyrilamine, 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

Complicated Urinary Tract Infection and Pyelonephritis – Efficacy in Pediatric Patients:

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.
Ciprofloxacin, administered I.V. and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) and pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety.
Patients were evaluated for clinical success and bacteriological eradication of the baseline organism(s) with no new infection or superinfection at 5 to 9 days post-therapy (Test of Cure or TOC). The Per Protocol population had a causative organism(s) with protocol specified colony count(s) at baseline, no protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population were similar between ciprofloxacin and the comparator group as shown below.

Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	CIPRO	**Comparator**
Randomized Patients	337	352
Per Protocol Patients	211	231
Clinical Response at 5 to 9 Days Post-Treatment	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]		
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [-1.3%, 13.1%]		
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)

* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.

INHALATIONAL ANTHRAX IN ADULTS AND PEDIATRICS – 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 LD_{50} (~5.5 x 10^5 spores (range 5-30 LD_{50}) 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.[6]

More than 9300 persons were recommended to complete a minimum of 60 days of antibiotic prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. Ciprofloxacin was recommended to most of those individuals for all or part of the prophylaxis regimen. Some persons were also given anthrax vaccine or were switched to alternative antibiotics. No one who received ciprofloxacin or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received ciprofloxacin as all or part of their post-exposure prophylaxis regimen is unknown.

Among the persons surveyed by the Centers for Disease Control and Prevention, over 1000 reported receiving ciprofloxacin as sole post-exposure prophylaxis for inhalational anthrax. Gastrointestinal adverse events (nausea, vomiting, diarrhea, or stomach pain), neurological adverse events (problems sleeping, nightmares, headache, dizziness or lightheadedness) and musculoskeletal adverse events (muscle or tendon pain and joint swelling or pain) were more frequent than had been previously reported in controlled clinical trials. This higher incidence, in the absence of a control group, could be explained by a reporting bias, concurrent medical conditions, other concomitant medications, emotional stress or other confounding factors, and/or a longer treatment period with ciprofloxacin. Because of these factors and limitations in the data collection, it is difficult to evaluate whether the reported symptoms were drug-related.

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.

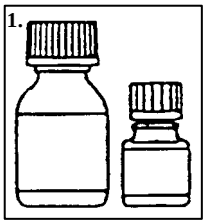
One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250 mg of ciprofloxacin.

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

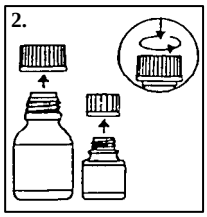
Appropriate Dosing Volumes of the Oral Suspensions:

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

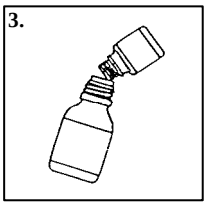
Preparation of the suspension:



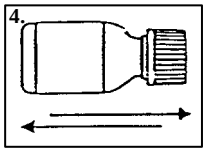
1. The small bottle contains the microcapsules, the large bottle contains the diluent.



2. Open both bottles. Child-proof cap: Press down according to instructions on the cap while turning to the left.



3. Pour the microcapsules completely into the larger bottle of diluent. **Do not add water to the suspension.**



4. Remove the top layer of the diluent bottle label (to reveal the CIPRO Oral Suspension label). Close the large bottle completely according to the directions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

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:

1. 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. **2.** 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. **3.** 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). **5.** Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. J Infect Dis 1992; 166:1184-7. **6.** Friedlander AM, et al. Postexposure prophylaxis against experimental inhalational anthrax. J Infect Dis 1993; 167:1239-42. **7.** Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195. **8.** Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6):1336-1339. **9.** Schaefer C, Amoura-Elefant E, Vial 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.

CIPRO® XR

(ciprofloxacin* extended-release tablets)

WARNING:
Fluoroquinolones, including CIPRO® XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

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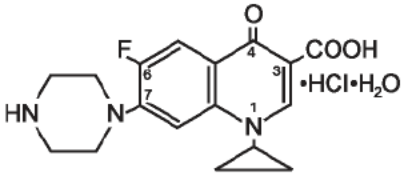
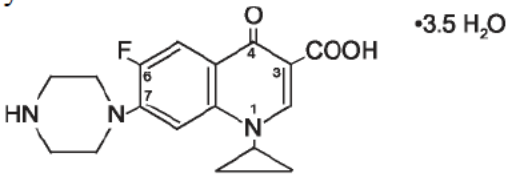
To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO® XR and other antibacterial drugs, CIPRO XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

CIPRO XR (ciprofloxacin* extended-release tablets) contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO XR tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the monohydrate and the sesquihydrate. The empirical formula of the monohydrate is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its molecular weight is 385.8. The empirical formula of the sesquihydrate is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot 1.5\ H_2O$ and its molecular weight is 394.8. The drug substance is a faintly yellowish to light yellow crystalline substance. The chemical structure of the monohydrate is as follows:



Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. As a hydrate, its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot 3.5\ H_2O$ and its molecular weight is 394.3. It is a pale yellowish to light yellow crystalline substance and its chemical structure is as follows:



CIPRO XR is available in 500 mg and 1000 mg (ciprofloxacin equivalent) tablet strengths. CIPRO XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. Each CIPRO XR 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (212.6 mg, calculated on the dried basis). Each CIPRO XR 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (425.2 mg, calculated on the dried basis). The inactive ingredients are crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.

* as ciprofloxacin† and ciprofloxacin hydrochloride

† does not comply with the loss on drying test and residue on ignition test of the USP monograph.

CLINICAL PHARMACOLOGY

Absorption

CIPRO XR tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.
The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO XR Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg•h/L)	$T_{1/2}$ (hr)	T_{max} (hr) §
CIPRO XR 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 – 4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 – 3.5)

§ median (range)
Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered with or without food (e.g. high-fat and low-fat meals or under fasted conditions).

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. 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. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug (see **CONTRAINDICATIONS**; **WARNINGS**; **PRECAUTIONS: Drug Interactions**).

Elimination

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin,

approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. 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 immediate-release 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 with the immediate-release tablet, 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 of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Pharmacokinetic studies of the immediate-release oral tablet (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. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which 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. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q24h in patients with creatinine clearance below 30 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

In studies in patients with stable chronic 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. (See **DOSAGE AND ADMINISTRATION**.)

Drug-drug Interactions

Concomitant administration with tizanidine is contraindicated. **(**See **CONTRAINDICATIONS).** Previous studies with immediate-release ciprofloxacin have shown that 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. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc. (See **WARNINGS: PRECAUTIONS, Drug Interactions** and **Information for Patients,** and **DOSAGE AND ADMINISTRATION**.)

Antacids: When CIPRO XR given as a single 1000 mg dose was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See **PRECAUTIONS, Information for Patients** and **Drug Interactions,** and **DOSAGE AND ADMINISTRATION**.)

Omeprazole: When CIPRO XR was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined. (See **PRECAUTIONS, Drug Interactions**.)

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to $1x10^{-6}$.

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.

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus saprophyticus

Aerobic gram-negative microorganisms

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

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

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of CIPRO XR in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms

Citrobacter koseri
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Susceptibility Tests

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

For testing *Enterobacteriaceae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus:*

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

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 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:

Microorganism		MIC Range (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25 – 2.0
Escherichia coli	ATCC 25922	0.004 – 0.015
Staphylococcus aureus	ATCC 29213	0.12 – 0.5
Pseudomonas aeruginosa	ATCC 27853	0.25 – 1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] 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 *Enterobacteriaceae, Enterococcus faecalis, Pseudomonas aeruginosa,* and *Staphylococcus saprophyticus*:

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

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:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	30 – 40
Staphylococcus aureus	ATCC 25923	22 – 30
Pseudomonas aeruginosa	ATCC 27853	25 – 33

INDICATIONS AND USAGE

CIPRO XR is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms as listed below. CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli, Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus* [a].

Complicated Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis,* or *Pseudomonas aeruginosa* [a].

Acute Uncomplicated Pyelonephritis caused by *Escherichia coli*.
[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED. 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 XR may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO XR and other antibacterial drugs, CIPRO XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS**: **Drug Interactions**.)

WARNINGS

Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO XR should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

THE SAFETY AND EFFECTIVENESS OF CIPRO XR IN PEDIATRIC PATIENTS AND 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.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs

revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Cytochrome P450 (CYP450): Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g. theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug.

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.

Other 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 ciprofloxacin. 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, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to

overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

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**.)
Photosensitivity/Phototoxicity: Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (See **ADVERSE REACTIONS and ADVERSE REACTIONS/ Post-Marketing Adverse Events).**
Prescribing CIPRO XR in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients:

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO XR treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- that antibacterial drugs including CIPRO XR should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO XR is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the

full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO XR or other antibacterial drugs in the future.

- that CIPRO XR may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration with magnesium/aluminum antacids, or sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or with other products containing calcium, iron, or zinc should be avoided. CIPRO XR may be taken two hours before or six hours after taking these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.) CIPRO XR 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, CIPRO XR may be taken with a meal that contains these products. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS, Drug Interactions**.)
- if the patient should forget to take CIPRO XR at the usual time, he/she may take the dose later in the day. Do not take more than one CIPRO XR tablet per day even if a patient misses a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**
- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue CIPRO XR at the first sign of a skin rash or other allergic reaction.
- that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.
- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- that CIPRO XR 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 increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- that CIPRO XR 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 CIPRO XR if there is a history of this condition.
- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions: In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

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, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients,** and **DOSAGE AND ADMINISTRATION**.)
Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.
Absorption of the CIPRO XR tablet was slightly diminished (20%) when given concomitantly with omeprazole. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**.)
Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.
The concomitant administration of ciprofloxacin with the sulfonylurea 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 significantly accelerates the absorption of oral ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.
Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.
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 V_{79} 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
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2 and 3 -fold greater than the 1000 mg daily human dose based upon body surface area).
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 the maximum recommended daily human dose of 1000 mg based upon mg/m^2), 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.
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 (1.0 times the highest recommended daily human dose of 1000 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 TERIS - 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 there is no risk.
A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. 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 549 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. However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for the 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 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 (0.7 and 0.4 times the maximum daily human dose of 1000 mg 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.

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 of CIPRO XR in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO XR. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO XR to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO XR and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

In a large, prospective, randomized CIPRO XR clinical trial in complicated urinary tract infections, 49% (509/1035) of the patients were 65 and over, while 30% (308/1035) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and clinical experience with other formulations of ciprofloxacin has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals 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**.)

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO XR with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500 mg or 1000 mg CIPRO XR. Most adverse events reported were described as mild to moderate in severity and required no treatment. The overall incidence, type and distribution of adverse events were similar in patients receiving both 500 mg and 1000 mg of CIPRO XR. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In the clinical trial of uncomplicated urinary tract infection, CIPRO XR (500 mg once daily) in 444 patients was compared to ciprofloxacin immediate-release tablets (250 mg twice daily) in 447 patients for 3 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 0.2% (1/444) of patients in the CIPRO XR arm and in 0% (0/447) of patients in the control arm.

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyelonephritis, CIPRO XR (1000 mg once daily) in 517 patients was compared to ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7 to 14 days. Discontinuations due to adverse reactions

thought to be drug-related occurred in 3.1% (16/517) of patients in the CIPRO XR arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the CIPRO XR arm were nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

In these clinical trials, the following events occurred in ≥ 2% of all CIPRO XR patients, regardless of drug relationship: nausea (4%), headache (3%), dizziness (2%), diarrhea (2%), vomiting (2%) and vaginal moniliasis (2%).

Adverse events, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of all CIPRO XR treated patients were: nausea (3%), diarrhea (2%), headache (1%), dyspepsia (1%), dizziness (1%), and vaginal moniliasis (1%). Vomiting (1%) occurred in the 1000 mg group.

Additional uncommon events, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of CIPRO XR treated patients were:

BODY AS A WHOLE: abdominal pain, asthenia, malaise, photosensitivity reaction

CARDIOVASCULAR: bradycardia, migraine, syncope

DIGESTIVE: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst

HEMIC/LYMPHATIC: prothrombin decrease

CENTRAL NERVOUS SYSTEM: abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

METABOLIC: hyperglycemia

SKIN/HYPERSENSIVITY: dry skin, maculopapular rash, photosensitivity/phototoxicity reactions, pruritus, rash, skin disorder, urticaria, vesiculobullous rash

SPECIAL SENSES: diplopia, taste perversion

UROGENITAL: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

The following additional adverse events, some of them life threatening, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications). Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure. The events in alphabetical order are:

abnormal gait, achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions and including life-threatening anaphylactic shock), amylase increase, anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C. difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, chromatopsia, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, fixed eruptions, flushing, gastrointestinal bleeding, gout (flare up), grand mal convulsion, gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic failure (including fatal cases), hepatic necrosis, hepatitis, hiccup, hyperesthesia, hyperpigmentation, hypertension, hypertonia, hypesthesia, hypotension, ileus, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lipase increase, lymphadenopathy, manic reaction, marrow depression, migraine, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, extremities, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, pancytopenia, paranoia, paresthesia, peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, photosensitivity/phototoxicity reaction, pleural effusion, polyuria, postural hypotension, prothrombin time prolongation, pseudomembranous colitis (the onset of symptoms may occur during or after antimicrobial treatment), pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, serum sickness-like reaction, Stevens-Johnson syndrome, sweating, tachycardia, taste loss, tendinitis, tendon

rupture, tinnitus, torsade de pointes, toxic epidermal necrolysis (Lyell's syndrome), toxic psychosis, twitching, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

Laboratory Changes:
The following adverse laboratory changes, in alphabetical order, regardless of incidence or relationship to drug, have been reported in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications):
Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts, prothrombin time, serum albumin, serum potassium, total serum protein, uric acid.
Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving theophylline concomitantly), serum triglycerides, uric acid.
Others: albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs, leukocytosis, methemoglobinemia, pancytopenia.

OVERDOSAGE

In the event of acute excessive 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.
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.
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 hypoactivity 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.

DOSAGE AND ADMINISTRATION

CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Cipro XR should be administered orally once daily as described in the following Dosage Guidelines table:

DOSAGE GUIDELINES

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days
Complicated Urinary Tract Infection	1000 mg	Q24h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg	Q24h	7-14 Days

Patients whose therapy is started with CIPRO I.V. for urinary tract infections may be switched to CIPRO XR when clinically indicated at the discretion of the physician.
CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration

with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. A 2-hour window between substantial calcium intake (> 800 mg) and dosing with CIPRO XR is recommended. CIPRO XR should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.** (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Drug Interactions** and **Information for Patients**.**)**

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 alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of < 30 mL/min, the dose of CIPRO XR should be reduced from 1000 mg to 500 mg daily. For patients on hemodialysis or peritoneal dialysis, administer CIPRO XR after the dialysis procedure is completed. (See **CLINICAL PHARMACOLOGY, Special Populations,** and **PRECAUTIONS, Geriatric Use**.)

Impaired Hepatic Function:
No dosage adjustment is required with CIPRO XR in patients with stable chronic cirrhosis. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **CLINICAL PHARMACOLOGY, Special Populations**.)

HOW SUPPLIED

CIPRO XR is available as nearly white to slightly yellowish, film-coated, oblong-shaped tablets containing 500 mg or 1000 mg ciprofloxacin. The 500 mg tablet is coded with the word "BAYER" on one side and "C500 QD" on the reverse side. The 1000 mg tablet is coded with the word "BAYER" on one side and "C1000 QD" on the reverse side.

	Strength	NDC Code
Bottles of 50	500 mg	0085-1775-02
Bottles of 100	500 mg	0085-1775-01
Bottles of 50	1000 mg	0085-1778-03
Bottles of 100	1000 mg	0085-1778-01
Unit Dose Pack of 30	1000 mg	0085-1778-02

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

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.
Crystalluria, 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, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria 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 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 Urinary Tract Infections (acute cystitis)

CIPRO XR was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled clinical trial conducted in the US. This study compared CIPRO XR (500 mg once daily for three days) with ciprofloxacin immediate-release tablets (CIPRO® 250 mg BID for three days). Of the 905 patients enrolled, 452 were randomly assigned to the CIPRO XR treatment group and 453 were randomly assigned to the control group. The primary efficacy variable was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at test-of-cure (Day 4 -11 Post-therapy).

The bacteriologic eradication and clinical success rates were similar between CIPRO XR and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO XR minus control group) are given in the following table:

	CIPRO XR 500 mg QD x 3 Days	**CIPRO 250 mg BID x 3 Days**
Randomized Patients	452	453
Per Protocol Patients†	199	223
Bacteriologic Eradication at TOC (n/N)*	188/199 (94.5%)	209/223 (93.7%)
	CI [-3.5%, 5.1%]	
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E. coli	156/160 (97.5%)	176/181 (97.2%)
E. faecalis	10/11 (90.9%)	17/21 (81.0%)
P. mirabilis	11/12 (91.7%)	7/7 (100%)
S. saprophyticus	6/7 (85.7%)	9/9 (100%)
Clinical Response at TOC (n/N)***	189/199 (95.0%)	204/223 (91.5%)
	CI [-1.1%, 8.1%]	

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/ total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

*** n/N = patients with clinical success /total number of patients

† The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria, except for *S. saprophyticus* ($\geq 10^4$ CFU/mL).

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

CIPRO XR was evaluated for the treatment of complicated urinary tract infections (cUTI) and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled clinical trial conducted in the US and Canada. The study enrolled 1,042 patients (521 patients per treatment arm) and compared CIPRO XR (1000 mg once daily for 7 to 14 days) with immediate-release ciprofloxacin (500 mg BID for 7 to 14 days). The primary efficacy endpoint for this trial was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at 5 to 11 days post-therapy (test-of-cure or TOC) for the Per Protocol and Modified Intent-To-Treat (MITT) populations.

The Per Protocol population was defined as patients with a diagnosis of cUTI or AUP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, no inclusion criteria violation, a valid test-of-cure urine culture within the TOC window, an organism susceptible to study drug, no premature discontinuation or loss to follow-up, and compliance with the dosage regimen (among other criteria).

More patients in the CIPRO XR arm than in the control arm were excluded from the Per Protocol population and this should be considered in the interpretation of the study results. Reasons for exclusion with the greatest discrepancy between the two arms were no valid test-of-cure urine culture, an organism resistant to the study drug, and premature discontinuation due to adverse events.

An analysis of all patients with a causative organism(s) isolated at baseline and who received study medication, defined as the MITT population, included 342 patients in the CIPRO XR arm and 324 patients in the control arm. Patients with missing responses were counted as failures in this analysis. In the MITT analysis of cUTI patients, bacteriologic eradication was 160/271 (59.0%) versus 156/248 (62.9%) in CIPRO XR and control arm, respectively [97.5% CI* (-13.5%, 5.7%)]. Clinical cure was 184/271 (67.9%) for CIPRO XR and 182/248 (73.4%) for control arm, respectively [97.5% CI* (-14.4%, 3.5%)]. Bacterial eradication in the MITT analysis of patients with AUP at TOC was 47/71 (66.2%) and 58/76 (76.3%) for CIPRO XR and control arm, respectively [97.5% CI* (-26.8%, 6.5%)]. Clinical cure at TOC was 50/71 (70.4%) for CIPRO XR and 58/76 (76.3%) for the control arm [97.5% CI* (-22.0%, 10.4%)].

* confidence interval of the difference in rates (CIPRO XR minus control).

In the Per Protocol population, the differences between CIPRO XR and the control arm in bacteriologic eradication rates at the TOC visit were not consistent between AUP and cUTI patients. The bacteriologic eradication rate for cUTI patients was higher in the CIPRO XR arm than in the control arm. For AUP patients, the bacteriologic eradication rate was lower in the CIPRO XR arm than in the control arm. This inconsistency was not observed between the two treatment groups for clinical cure rates. Clinical cure rates were 96.1% (198/206) and 92.1% (211/229) for CIPRO XR and the control arm, respectively.

The bacterial eradication and clinical cure rates by infection type for CIPRO XR and the control arm at the TOC visit and their corresponding 97.5% confidence intervals for the differences between rates (CIPRO XR minus control arm) are given below for the Per Protocol population analysis:

	CIPRO XR 1000 mg QD	**CIPRO 500 mg BID**
Randomized Patients	521	521
Per Protocol Patients^	206	229
cUTI Patients		
Bacteriologic Eradication at TOC (n/N)*	148/166 (89.2%)	144/177 (81.4%)
	CI [-0.7%, 16.3%]	
Bacteriologic Eradication (by organism) at TOC (n/N)**		
E. coli	91/94 (96.8%)	90/92 (97.8%)
K. pneumoniae	20/21 (95.2%)	19/23 (82.6%)
E. faecalis	17/17 (100%)	14/21 (66.7%)
P. mirabilis	11/12 (91.6%)	10/10 (100%)
P. aeruginosa	3/3 (100%)	3/3 (100%)
Clinical Cure at TOC (n/N)***	159/166 (95.8%)	161/177 (91.0%)
	CI [-1.1%, 10.8%]	
AUP Patients		
Bacteriologic Eradication at TOC (n/N)*	35/40 (87.5%)	51/52 (98.1%)
	CI [-34.8%, 6.2%]	
Bacteriologic Eradication of *E. coli* at TOC (n/N)**	35/36 (97.2%)	41/41 (100%)
Clinical Cure at TOC (n/N)***	39/40 (97.5%)	50/52 (96.2%)
	CI [-15.3%, 21.1%]	

^ Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at baseline or no organism present at ≥ 10^5 CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an adverse event, lost to follow-up, or non-compliance with dosage regimen (among other criteria).

* n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total number of patients

** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

***n/N = patients with clinical success /total number of patients

Of the 166 cUTI patients treated with CIPRO XR, 148 (89%) had the causative organism(s) eradicated, 8 (5%) had persistence, 5 (3%) patients developed superinfections and 5 (3%) developed new infections. Of the 177 cUTI patients treated in the control arm, 144 (81%) had the causative organism(s) eradicated, 16 (9%) patients had persistence, 3 (2%) developed superinfections and 14 (8%) developed new infections. Of the 40 patients with AUP treated with CIPRO XR, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had persistence and 3 (7.5%) developed new infections. Of the 5 CIPRO XR AUP patients without eradication at TOC, 4 were considered clinical cures and did not receive alternative antibiotic therapy. Of the 52 patients with AUP treated in the control arm, 51 (98%) had the causative organism(s) eradicated. One patient (2%) had persistence.

References: 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.

2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

CIPRO® I.V.
(ciprofloxacin)
For Intravenous Infusion

WARNING:
Fluoroquinolones, including CIPRO I.V., are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

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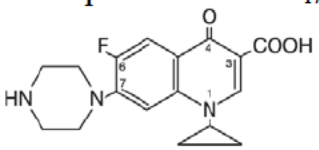
To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO® I.V. and other antibacterial drugs, CIPRO I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

CIPRO I.V. (ciprofloxacin) is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is:



Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol. CIPRO I.V. solutions are available as sterile 1.0% aqueous concentrates, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulas contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrates in vials is 3.3 to 3.9. The pH range for the 0.2% ready-for-use infusion solutions is 3.5 to 4.6.

The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di(2-ethylhexyl) phthalate (DEHP), up to 5 parts per million. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Absorption

Following 60-minute intravenous infusions of 200 mg and 400 mg ciprofloxacin to normal volunteers, the mean maximum serum concentrations achieved were 2.1 and 4.6 µg/mL, respectively; the concentrations at 12 hours were 0.1 and 0.2 µg/mL, respectively.

Steady-state Ciprofloxacin Serum Concentrations (µg/mL)
After 60-minute I.V. Infusions q 12 h.

	Time after starting the infusion					
Dose	**30 min.**	**1 hr**	**3 hr**	**6 hr**	**8 hr**	**12 hr**
200 mg	1.7	2.1	0.6	0.3	0.2	0.1
400 mg	3.7	4.6	1.3	0.7	0.5	0.2

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. Comparison of the pharmacokinetic parameters following the 1st and 5th I.V. dose on a q 12 h regimen indicates no evidence of drug accumulation.
The absolute bioavailability of oral ciprofloxacin is within a range of 70–80% with no substantial loss by first pass metabolism. An intravenous infusion of 400-mg ciprofloxacin given over 60 minutes every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500-mg oral dose given every 12 hours. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750-mg oral dose given every 12 hours. A 400-mg I.V. dose results in a C_{max} similar to that observed with a 750-mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250-mg oral dose given every 12 hours.

Steady-state Pharmacokinetic Parameter 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 (μg•hr/mL)	13.7 [a]	12.7 [a]	31.6 [b]	32.9 [c]
C_{max} (μg/mL)	2.97	4.56	3.59	4.07

[a] $AUC_{0\text{-}12h}$
[b] $AUC\ 24h = AUC_{0\text{-}12h} \times 2$
[c] $AUC\ 24h = AUC_{0\text{-}8h} \times 3$

Distribution
After intravenous administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous chambers of the eye are lower than in serum.

Metabolism
After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The binding of ciprofloxacin to serum proteins is 20 to 40%. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug (see **CONTRAINDICATIONS**; **WARNINGS**; **PRECAUTIONS: Drug Interactions**).

Excretion
The serum elimination half-life is approximately 5–6 hours and the total clearance is around 35 L/hr. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg I.V. dose, concentrations in the urine usually exceed 200 μg/mL 0–2 hours after dosing and are generally greater than 15 μg/mL 8–12 hours after dosing. Following a 400-mg I.V. dose, urine concentrations generally exceed 400 μg/mL

0–2 hours after dosing and are usually greater than 30 µg/mL 8–12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (< 1%) is recovered from the bile as unchanged drug. Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing.

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 and dosage adjustments may be required. (See **DOSAGE AND ADMINISTRATION**.)

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

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 µg/mL (range: 1.5 – 3.4 µg/mL) and the mean AUC was 9.2 µg*h/mL (range: 5.8 – 14.9 µg*h/mL). There was no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg TID).

In children with severe sepsis who were given intravenous ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 µg/mL (range: 4.6 – 8.3 µg/mL) in 10 children less than 1 year of age; and 7.2 µg/mL (range: 4.7 – 11.8 µg/mL) in 10 children between 1 and 5 years of age. The AUC values were 17.4 µg*h/mL (range: 11.8 – 32.0 µg*h/mL) and 16.5 µg*h/mL (range: 11.0 – 23.8 µg*h/mL) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4 - 5 hours, and the bioavailability of the oral suspension is approximately 60%.

Drug-drug Interactions: Concomitant administration with tizanidine is contraindicated **(**See **CONTRAINDICATIONS).** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **WARNINGS: PRECAUTIONS: Drug Interactions**.)

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 vitro* 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 I.V. (ciprofloxacin for intravenous infusion).

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)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

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 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin intravenous formulations 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)

Aerobic gram-negative microorganisms

Acinetobacter Iwoffi	*Salmonella typhi*
Aeromonas hydrophila	*Shigella boydii*
Campylobacter jejuni	*Shigella dysenteriae*
Edwardsiella tarda	*Shigella flexneri*
Enterobacter aerogenes	*Shigella sonnei*
Klebsiella oxytoca	*Vibrio cholerae*
Legionella pneumophila	*Vibrio parahaemolyticus*
Neisseria gonorrhoeae	*Vibrio vulnificus*
Pasteurella multocida	*Yersinia enterocolitica*
Salmonella enteritidis	

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 method[1] (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 *Enterobacteriaceae, Enterococcus faecalis,* methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes,* and *Pseudomonas aeruginosa*[a]:

MIC (µg/mL)	Interpretation	
≤ 1	Susceptible	(S)
2	Intermediate	(I)
≥ 4	Resistant	(R)

[a] These 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* [b]:

MIC (µg/mL)	Interpretation	
≤ 1	Susceptible	(S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

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.

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 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		MIC (µg/mL)
E. faecalis	ATCC 29212	0.25 – 2.0
E. coli	ATCC 25922	0.004 – 0.015
H. influenzae[a]	ATCC 49247	0.004 – 0.03
P. aeruginosa	ATCC 27853	0.25 – 1.0
S. aureus	ATCC 29213	0.12 – 0.5

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] 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 *Enterobacteriaceae*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* [a]:

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

[a] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [b]:

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

[b] 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.

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		Zone Diameter (mm)
E. coli	ATCC 25922	30-40
H. influenzae [a]	ATCC 49247	34-42
P. aeruginosa	ATCC 27853	25-33
S. aureus	ATCC 25923	22-30

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

INDICATIONS AND USAGE

CIPRO I.V. is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below when the intravenous administration offers a route of administration advantageous to the patient. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Adult Patients:

Urinary Tract Infections caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Lower Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or penicillin-susceptible *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*.

Nosocomial Pneumonia caused by *Haemophilus influenzae* or *Klebsiella pneumoniae.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *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 conjunction with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

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

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

Empirical Therapy for Febrile Neutropenic Patients in combination with piperacillin sodium. (See **CLINICAL STUDIES**.)

Pediatric patients (1 to 17 years of age):

Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli*.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

Adult and Pediatric Patients:

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

Ciprofloxacin serum concentrations achieved in humans served as a surrogate endpoint reasonably likely to predict clinical benefit and provided the initial basis for approval of this indication.[4] Supportive clinical information for ciprofloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001. (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

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 I.V. 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO I.V. and other antibacterial drugs, CIPRO I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS**: **Drug Interactions**.)

WARNINGS

Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO I.V., are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of

developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO I.V. should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Pregnant Women: THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pregnancy,** and **Nursing Mothers** subsections.)

Pediatrics: Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS**.)
In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Cytochrome P450 (CYP450): Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g. theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug.

Central Nervous System Disorders: 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 Interaction** and **ADVERSE REACTIONS.**)

Theophylline: SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF INTRAVENOUS CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure,

status epilepticus, and respiratory failure. Although similar serious adverse events 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.

Hypersensitivity Reactions: 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 and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Other 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 ciprofloxacin. 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, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**).

Pseudomembranous Colitis: *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin.

Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

PRECAUTIONS

General: INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local I.V. site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See **ADVERSE REACTIONS**.)

Central Nervous System: 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.**)

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.

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

Photosensitivity/Phototoxicity: Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (See **ADVERSE REACTIONS and ADVERSE REACTIONS/ Post-Marketing Adverse Events).**

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

Prescribing CIPRO I.V. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information For Patients:

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO I.V. treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- that antibacterial drugs including CIPRO I.V. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO I.V. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO I.V. or other antibacterial drugs in the future.
- 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.
- that photosensitivity/phototoxicity has been reported in patients receiving quinolones.

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.

- 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 increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- 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 ciprofloxacin.
- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.
- that ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See **WARNINGS, PRECAUTIONS, Pediatric Use** and **ADVERSE REACTIONS**.)
- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions: In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

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 prolongation of its serum half-life.

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

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, in some patients, resulted in severe hypoglycemia. Fatalities have been reported.

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

were given 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.

Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL $^1/_2$ hour and 1.18 µg/mL between 6–8 hours after the end of infusion.

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

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} 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, two of the eight tests were positive, but results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon mg/m^2).

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/m^2), 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.[3]

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 (approximately 0.7-times the highest recommended therapeutic dose based upon mg/m^2) 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 TERIS – 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.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] 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 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] 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.[7,8] 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, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic dose based upon mg/m^2) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced 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: Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL PHARMACOLOGY**.)

Inhalational Anthrax (Post-Exposure)
Ciprofloxacin is indicated in pediatric patients for 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**.

Complicated Urinary Tract Infection and Pyelonephritis
Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli.* Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including those related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within six weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Cystic Fibrosis
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 I.V. 10 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 I.V. 50 mg/kg/dose q8h and tobramycin I.V. 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.
Musculoskeletal adverse events in patients with cystic fibrosis 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. Other adverse events were similar in nature and frequency between treatment arms. 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 can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.
Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO I.V. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO I.V. to elderly patients especially those on corticosteroids. Patients should be informed

of this potential side effect and advised to discontinue CIPRO I.V. and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

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**.)

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Adverse Reactions in Adult Patients: 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 1.8% of intravenously 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%).

In clinical trials the following events were reported, regardless of drug relationship, in greater than 1% of patients treated with intravenous ciprofloxacin: nausea, diarrhea, central nervous system disturbance, local I.V. site reactions, liver function tests abnormal, eosinophilia, headache, restlessness, and rash. Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Local I.V. site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Additional medically important events, without regard to drug relationship or route of administration, that occurred in 1% or less of ciprofloxacin patients are listed below:

BODY AS A WHOLE: abdominal pain/discomfort, foot pain, pain, pain in extremities

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine

CENTRAL NERVOUS SYSTEM: convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, abnormal gait, grand mal convulsion, anorexia

GASTROINTESTINAL: ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric pain, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, hepatitis, painful oral mucosa

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis

RENAL/UROGENITAL: renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.

RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, laryngeal or pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, bronchospasm

SKIN/HYPERSENSITIVITY: allergic reactions, anaphylactic reactions including life-threatening anaphylactic shock, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity/phototoxicity reaction (See **WARNINGS**.)

SPECIAL SENSES: decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, chromatopsia, a bad taste

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 (I.V. and I.V./P.O. sequential) with intravenous beta-lactam control antibiotics, the CNS adverse event profile of ciprofloxacin was comparable to that of the control drugs.

Adverse Reactions in Pediatric Patients: Ciprofloxacin, administered I.V. and /or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received I.V. or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC

	Ciprofloxacin	**Comparator**
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval*	(-0.8%, +7.2%)	
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, +9.1%)	

*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence interval indicated that it could not be concluded that the ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or post-marketing experience may also occur in pediatric patients.

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, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), photosensitivity/phototoxicity reaction, 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, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

Adverse events were also reported by persons who received ciprofloxacin for anthrax post-exposure prophylaxis following the anthrax bioterror attacks of October 2001 (See also **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

Adverse Laboratory Changes: The most frequently reported changes in laboratory parameters with intravenous ciprofloxacin therapy, without regard to drug relationship are listed below:

Hepatic	—	elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, and serum bilirubin
Hematologic	—	elevated eosinophil and platelet counts, decreased platelet counts, hemoglobin and/or hematocrit
Renal	—	elevations of serum creatinine, BUN, and uric acid
Other	—	elevations of serum creatine phosphokinase, serum theophylline (in patients receiving theophylline concomitantly), blood glucose, and triglycerides

Other changes occurring infrequently were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of serum gamma-glutamyl transpeptidase (γ GT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol. Other changes occurring rarely during administration of ciprofloxacin were: elevation of serum amylase, decrease of blood glucose, pancytopenia, leukocytosis, elevated sedimentation rate, change in serum phenytoin, decreased prothrombin time, hemolytic anemia, and bleeding diathesis.

OVERDOSAGE

In the event of acute overdosage, the patient should be carefully observed and given supportive treatment, including monitoring of renal function. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

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 - ADULTS

CIPRO I.V. should be administered to adults by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See **Preparation of CIPRO I.V. for Administration** section.)

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

ADULT DOSAGE GUIDELINES

Infection†	Severity	Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10-14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe			7-14 Days
	Ciprofloxacin	400 mg	q8h	
	+			
	Piperacillin	50 mg/kg Not to exceed 24 g/day	q4h	
Inhalational anthrax (post-exposure)**		400 mg	q12h	60 Days

*****used in conjunction with metronidazole. (See product labeling for prescribing information.)

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

** 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.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**. Total duration of ciprofloxacin administration (I.V. or oral) for inhalational anthrax (post-exposure) is 60 days.

CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes.

Conversion of I.V. to Oral Dosing in Adults: CIPRO Tablets and CIPRO Oral Suspension for oral administration are available. Parenteral therapy may be switched to oral CIPRO when the condition warrants, at the discretion of the physician. (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens.)

Equivalent AUC Dosing Regimens

CIPRO Oral Dosage	Equivalent CIPRO 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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Adults with 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 for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dosage
> 30	See usual dosage.
5 - 29	200-400 mg q 18-24 hr

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 × the value calculated for men.

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

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, careful monitoring is suggested.

DOSAGE AND ADMINISTRATION - PEDIATRICS

CIPRO I.V. should be administered as described in the Dosage Guidelines table. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Dosing and initial route of therapy (i.e., I.V. or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6 to 10 mg/kg I.V. every 8 hours and allowed to switch to oral therapy (10 to 20 mg/kg every 12 hours), at the discretion of the physician.

PEDIATRIC DOSAGE GUIDELINES				
Infection	Route of Administration	Dose (mg/kg)	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)	Intravenous	6 to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 8 hours	10-21 days*
	Oral	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 12 hours	
Inhalational Anthrax (Post-Exposure) **	Intravenous	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
	Oral	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	

* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).

** Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (i.e., creatinine clearance of < 50 mL/min/1.73m^2).

Preparation of CIPRO I.V. for Administration

Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED BEFORE USE. The intravenous dose should be prepared by aseptically withdrawing the concentrate from the vial of CIPRO I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1–2mg/mL. (See **COMPATIBILITY AND STABILITY**.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of CIPRO I.V. If the concomitant use of CIPRO I.V. and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Flexible Containers: CIPRO I.V. is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible containers do not need to be diluted and may be infused as described above.

COMPATIBILITY AND STABILITY

Ciprofloxacin injection 1% (10 mg/mL), when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL, is stable for up to 14 days at refrigerated or room temperature storage.

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Sterile Water for Injection
10% Dextrose for Injection
5% Dextrose and 0.225% Sodium Chloride for Injection
5% Dextrose and 0.45% Sodium Chloride for Injection
Lactated Ringer's for Injection

HOW SUPPLIED

CIPRO I.V. (ciprofloxacin) is available as a clear, colorless to slightly yellowish solution. CIPRO I.V. is available in 200 mg and 400 mg strengths. The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:

VIAL: manufactured for Bayer Pharmaceuticals Corporation by Bayer HealthCare LLC, Shawnee, Kansas.

SIZE	STRENGTH	NDC NUMBER
20 mL	200 mg, 1%	0085-1763-03
40 mL	400 mg, 1%	0085-1731-01

FLEXIBLE CONTAINER: manufactured for Bayer Pharmaceuticals Corporation by Hospira, Inc., Lake Forest, IL 60045.

SIZE	STRENGTH	NDC NUMBER
100 mL 5% Dextrose	200 mg, 0.2%	0085-1755-02
200 mL 5% Dextrose	400 mg, 0.2%	0085-1741-02

FLEXIBLE CONTAINER: manufactured for Bayer Pharmaceuticals Corporation by Baxter Healthcare Corporation, Deerfield, IL 60015.

SIZE	STRENGTH	NDC NUMBER
100 mL 5% Dextrose	200 mg, 0.2%	0085-1781-01
200 mL 5% Dextrose	400 mg, 0.2%	0085-1762-01

STORAGE

Vial: Store between 5 – 30ºC (41 – 86ºF).
Flexible Container: Store between 5 – 25ºC (41 – 77ºF).
Protect from light, avoid excessive heat, protect from freezing.
Ciprofloxacin is also available as CIPRO (ciprofloxacin HCl) Tablets 250, 500, and 750 mg and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.
* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

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 young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3- and 3.5-times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, 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, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single oral doses as low as 5 mg/kg (approximately 0.07-times the highest recommended therapeutic dose based upon mg/m^2). 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 (approximately 0.2-times the highest recommended therapeutic dose based upon mg/m^2).

In dogs, ciprofloxacin administered at 3 and 10 mg/kg by rapid intravenous injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release because they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid intravenous 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.

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 LD_{50} (~5.5 x 10^5) spores (range 5–30 LD_{50}) 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.[6]

More than 9300 persons were recommended to complete a minimum of 60 days of antibiotic prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. Ciprofloxacin was recommended to most of those individuals for all or part of the prophylaxis regimen. Some persons were also given anthrax vaccine or were switched to alternative antibiotics. No one who received ciprofloxacin or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received ciprofloxacin as all or part of their post-exposure prophylaxis regimen is unknown.

Among the persons surveyed by the Centers for Disease Control and Prevention, over 1000 reported receiving ciprofloxacin as sole post-exposure prophylaxis for inhalational anthrax. Gastrointestinal adverse events (nausea, vomiting, diarrhea, or stomach pain), neurological adverse events (problems sleeping, nightmares, headache, dizziness or lightheadedness) and musculoskeletal adverse events (muscle or tendon pain and joint swelling or pain) were more frequent than had been previously reported in controlled clinical trials. This higher incidence, in the absence of a control group, could be explained by a reporting bias, concurrent medical conditions, other concomitant medications, emotional stress or other confounding factors, and/or a longer treatment period with ciprofloxacin. Because of these factors and limitations in the data collection, it is difficult to evaluate whether the reported symptoms were drug-related.

CLINICAL STUDIES

EMPIRICAL THERAPY IN ADULT FEBRILE NEUTROPENIC PATIENTS

The safety and efficacy of ciprofloxacin, 400 mg I.V. q 8h, in combination with piperacillin sodium, 50 mg/kg I.V. q 4h, for the empirical therapy of febrile neutropenic patients were studied in one large pivotal multicenter, randomized trial and were compared to those of tobramycin, 2 mg/kg I.V. q 8h, in combination with piperacillin sodium, 50 mg/kg I.V. q 4h.

Clinical response rates observed in this study were as follows:

Outcomes	Ciprofloxacin/Piperacillin N = 233 Success (%)		Tobramycin/Piperacillin N = 237 Success (%)	
Clinical Resolution of Initial Febrile Episode with No Modifications of Empirical Regimen*	63	(27.0%)	52	(21.9%)
Clinical Resolution of Initial Febrile Episode Including Patients with Modifications of Empirical Regimen	187	(80.3%)	185	(78.1%)
Overall Survival	224	(96.1%)	223	(94.1%)

* To be evaluated as a clinical resolution, patients had to have: (1) resolution of fever; (2) microbiological eradication of infection (if an infection was microbiologically documented); (3) resolution of signs/symptoms of infection; and (4) no modification of empirical antibiotic regimen.

Complicated Urinary Tract Infection and Pyelonephritis – Efficacy in Pediatric Patients:

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.

Ciprofloxacin, administered I.V. and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) and pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety.

Patients were evaluated for clinical success and bacteriological eradication of the baseline organism(s) with no new infection or superinfection at 5 to 9 days post-therapy (Test of Cure or TOC). The Per Protocol population had a causative organism(s) with protocol specified colony count(s) at baseline, no protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population were similar between ciprofloxacin and the comparator group as shown below.

Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	CIPRO	Comparator
Randomized Patients	337	352
Per Protocol Patients	211	231
Clinical Response at 5 to 9 Days Post-Treatment	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]		
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [-1.3%, 13.1%]		
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)

* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.

References:

1. 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. **2.** 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. **3.** Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Products 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). **5.** Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. J Infect Dis 1992; 166: 1184-7. **6.** Friedlander AM, et al. Postexposure prophylaxis against experimental inhalational anthrax. J Infect Dis 1993; 167: 1239-42. **7.** Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195. **8.** Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6): 1336-1339. **9.** Schaefer C, Amoura-Elefant E, Vial 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.

Manufactured for:

Bayer HealthCare

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516

Distributed by:

Schering-Plough

Schering Corporation
Kenilworth, NJ 07033

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MEDICATION GUIDE

CIPRO® *(Sip-row)*
(ciprofloxacin hydrochloride)
TABLETS

CIPRO® *(Sip-row)*
(ciprofloxacin)
ORAL SUSPENSION

CIPRO® XR *(Sip-row)*
(ciprofloxacin extended-release tablets)

CIPRO® I.V. *(Sip-row)*
(ciprofloxacin)
For Intravenous Infusion

Read the Medication Guide that comes with CIPRO before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CIPRO?
CIPRO belongs to a class of antibiotics called fluoroquinolones. CIPRO can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take CIPRO.

Tendon rupture or swelling of the tendon (tendinitis)

- Tendons are tough cords of tissue that connect muscles to bones.
- Pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including CIPRO. The risk of getting tendon problems is higher if you:
    - are over 60 years of age
    - are taking steroids (corticosteroids)
    - have had a kidney, heart, or lung transplant.
- Swelling of the tendon (tendinitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
- Other reasons for tendon ruptures can include:
    - physical activity or exercise
    - kidney failure
    - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
- Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking CIPRO until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of

tendon rupture with continued use of CIPRO. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.

- Tendon rupture can happen while you are taking or after you have finished taking CIPRO. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
    - hear or feel a snap or pop in a tendon area
    - bruising right after an injury in a tendon area
    - unable to move the affected area or bear weight
- See the section "**What are the possible side effects of CIPRO**?" for more information about side effects.

What is CIPRO?

CIPRO is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.

Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking CIPRO. CIPRO should not be used as the first choice of antibiotic medicine in children under 18 years of age. CIPRO Tablets, CIPRO Oral Suspension and CIPRO I.V. should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if CIPRO XR is safe and works in children under 18 years of age.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including CIPRO, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking CIPRO.

Who should not take CIPRO?

Do not take CIPRO if you:

- have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in CIPRO. Ask your healthcare provider if you are not sure. See the list of ingredients in CIPRO at the end of this Medication Guide.
- also take a medicine called tizanidine (Zanaflex®). Serious side effects from tizanidine are likely to happen.

What should I tell my healthcare provider before taking CIPRO?

See "**What is the most important information I should know about CIPRO?**"

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems

- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"
- have a history of seizures
- have kidney problems. You may need a lower dose of CIPRO if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- have trouble swallowing pills
- are pregnant or planning to become pregnant. It is not known if CIPRO will harm your unborn child.
- are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. You and your healthcare provider should decide whether you will take CIPRO or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. CIPRO and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take CIPRO or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of CIPRO?**".
- a blood thinner (warfarin, Coumadin®, Jantoven®)
- tizanidine (Zanaflex®) You should not take CIPRO if you are already taking tizanidine. See "**Who should not take CIPRO?**"
- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)
- glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®). See "**What are the possible side effects of CIPRO?**"
- phenytoin(Fosphenytoin Sodium®, Cerebyx®, Dilantin-125®, Dilantin®, Extended Phenytoin Sodium®, Prompt Penytoin Sodium®, Phenytek®)
- products that contain caffeine
- a medicine to control your heart rate or rhythm (antiarrhythmics) See "**What are the possible side effects of CIPRO?**"
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about CIPRO?**"
- methotrexate (Trexall®)
- Probenecid (Probalan®, Col-probenecid®)
- Metoclopromide (Reglan®, Reglan ODT®)
- Certain medicines may keep CIPRO Tablets, CIPRO Oral Suspension from working correctly. Take CIPRO Tablets and Oral Suspension either 2 hours before or 6 hours

after taking these products:

- an antacid, multivitamin, or other product that has magnesium, calcium, aluminum, iron, or zinc
- sucralfate (Carafate®)
- didanosine (Videx®, Videx® EC).

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take CIPRO?

- Take CIPRO exactly as prescribed by your healthcare provider.
- Take CIPRO Tablets in the morning and evening at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- Take CIPRO Oral Suspension in the morning and evening at about the same time each day. Shake the CIPRO Oral Suspension bottle well each time before use for about 15 seconds to make sure the suspension is mixed well. Close the bottle completely after use.
- Take CIPRO XR one time each day at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- CIPRO I.V. is given to you by intravenous (I.V.) infusion into your vein, slowly, over 60 minutes, as prescribed by your healthcare provider.
- CIPRO can be taken with or without food.
- CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking CIPRO.
- Do not skip any doses, or stop taking CIPRO even if you begin to feel better, until you finish your prescribed treatment, unless:
  - you have tendon effects (see "**What is the most important information I should know about CIPRO?**"),
  - you have a serious allergic reaction (see "**What are the possible side effects of CIPRO?**"), or
  - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to CIPRO. If this happens, CIPRO and other antibiotic medicines may not work in the future.
- If you miss a dose of CIPRO Tablets or Oral Suspension, take it as soon as you remember. Do not take two doses at the same time, and do not take more than two doses in one day.
- If you miss a dose of CIPRO XR, take it as soon as you remember. Do not take more than one dose in one day.

- If you take too much, call your healthcare provider or get medical help immediately.

If you have been prescribed CIPRO Tablets, CIPRO Oral Suspension or CIPRO I.V. after being exposed to anthrax:

- CIPRO Tablets, Oral Suspension and I.V. has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.
- Take CIPRO exactly as prescribed by your healthcare provider. Do not stop taking CIPRO without talking with your healthcare provider. If you stop taking CIPRO too soon, it may not keep you from getting the anthrax disease.
- Side effects may happen while you are taking CIPRO Tablets, Oral Suspension or I.V. When taking your CIPRO to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping CIPRO too soon are more important than the risks of side effects with CIPRO.
- If you are pregnant, or plan to become pregnant while taking CIPRO, you and your healthcare provider should decide whether the benefits of taking CIPRO Tablets, Oral Suspension or I.V. for anthrax are more important than the risks.

What should I avoid while taking CIPRO?

- CIPRO can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how CIPRO affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. CIPRO can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking CIPRO, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of CIPRO?

CIPRO can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about CIPRO?**"

Other serious side effects of CIPRO include:

- **Central Nervous System Effects:** Seizures have been reported in people who take fluoroquinolone antibiotics including CIPRO. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking CIPRO will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of CIPRO. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
  - feel dizzy
  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)

    - feel restless
    - tremors
    - feel anxious or nervous
    - confusion
    - depression
    - trouble sleeping
    - nightmares
    - feel more suspicious (paranoia)
    - suicidal thoughts or acts
- **Serious allergic reactions:** Allergic reactions can happen in people taking fluoroquinolones, including CIPRO, even after only one dose. Stop taking CIPRO and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
    - hives
    - trouble breathing or swallowing
    - swelling of the lips, tongue, face
    - throat tightness, hoarseness
    - rapid heartbeat
    - faint
    - yellowing of the skin or eyes. Stop taking CIPRO and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to CIPRO (a liver problem).
- **Skin rash:** Skin rash may happen in people taking CIPRO, even after only one dose. Stop taking CIPRO at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to CIPRO.
- **Serious heart rhythm changes** (QT prolongation and torsades de pointes): Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. CIPRO may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:
    - who are elderly
    - with a family history of prolonged QT interval,
    - with low blood potassium (hypokalemia),
    - who take certain medicines to control heart rhythm (antiarrhythmics).
- **Intestine infection** (Pseudomembranous colitis): Pseudomembranous colitis can happen with most antibiotics, including CIPRO. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy): Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including CIPRO. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

    - pain
    - burning
    - tingling
    - numbness
    - weakness

  CIPRO may need to be stopped to prevent permanent nerve damage.
- **Low blood sugar (hypoglycemia):** People who take CIPRO and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with CIPRO. Your antibiotic medicine may need to be changed.
- **Sensitivity to sunlight** (photosensitivity): See "**What should I avoid while taking CIPRO**?"
- **Joint Problems:** Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with CIPRO.

The most common side effects of CIPRO include:

- nausea
- headache
- diarrhea
- vomiting
- vaginal yeast infection
- changes in liver function tests
- pain or discomfort in the abdomen

These are not all the possible side effects of CIPRO. Tell your healthcare provider about any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CIPRO?

- CIPRO Tablets
    - Store CIPRO below 86°F (30°C).

- CIPRO Oral Suspension
    - Store CIPRO Oral Suspension below 86°F (30°C) for up to 14 days.
    - Do not freeze.
    - After treatment has been completed, any unused oral suspension should be safely thrown away.

- CIPRO XR
    - Store CIPRO XR at 59°F to 86°F (15°C to 30°C).

Keep CIPRO and all medicines out of the reach of children.

General Information about CIPRO
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CIPRO for a condition for which it is not prescribed. Do not give CIPRO to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about CIPRO. If you would like more information about CIPRO, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIPRO that is written for healthcare professionals. For more information go to www.CIPRO.com or call 1-800-526-4099.

What are the ingredients in CIPRO?

- CIPRO Tablets:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol.

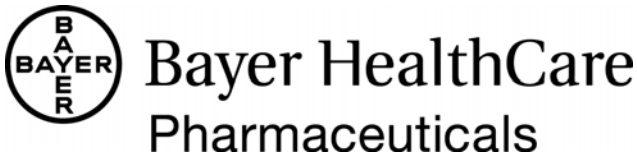
- CIPRO Oral Suspension:
  - Active ingredient: ciproflxacin
  - Inactive ingredients: The components of the suspension have the following compositions: Microcapsules—ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and Polysorbate 20. Diluent—medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

- CIPRO XR:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.

- CIPRO I.V.:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

Revised September 2008

Manufactured by:



Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Distributed by:

Schering Corporation
Kenilworth, NJ 07033

Rx Only
XXXXXXX, R.X 09/08
 Printed in U.S.A.
CIPRO (ciprofloxacin) 5% and 10% Oral Suspension Made in Italy
CIPRO (ciprofloxacin HCl) Tablets Made in Germany

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

OTHER REVIEW(S)

DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS (DSPTP)

Review by Deputy Division for Safety (DDS) of Labeling Supplements for Fluoroquinolone Class Labeling, including Medication Guides

Drug Names/NDAs:

- CIPRO® (ciprofloxacin hydrochloride) Tablets, NDA 19- 537/S-068
- CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-847/S-042
- CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-857/S-049
- CIPRO® (ciprofloxacin) Oral Suspension, NDA 20-780/S-026
- CIPRO® XR (ciprofloxacin extended-release tablets), NDA 21-473/S-024

Submission Date: August 5, 2008 (extension letter dated September 5, 2008)
Applicant: Bayer Pharmaceuticals Inc.

- Avelox (moxifloxacin hydrochloride) Tablets, NDA 21-085/S-040
- Avelox I.V. (moxifloxacin hydrochloride in NaCl injection), NDA 21-277/S-034

Submission Date: August 5, 2008 (extension letter dated September 5, 2008)
Applicant: Bayer Pharmaceuticals Inc.

- Proquin XR, NDA 21-744/S-008

Submission Date: August 7, 2008 (extension letter dated September 5, 2008)
Applicant/sponsor: Depomed

- Levaquin® (levofloxacin) Tablets, NDA 20-634/S-052
- Levaquin® (levofloxacin) Oral Solution, NDA 21-721/S-020
- Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, NDA 20-635/S-057

Submission Date: August 6, 2008 (extension letter dated September 5, 2008)
Applicant: Ortho McNeil-Janssen Pharmaceutical, Inc. c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

- Floxin Tablets (Ofloxacin Tablets), NDA 19-735/S-059

Submission Date: August 6, 2008 (extension letter dated September 5, 2008)
Applicant: Johnson & Johnson

- FACTIVE (gemifloxacin mesylate) Tablets, NDA 21-158/S-012

Submission Date: August 4, 2008 (extension letter dated September 5, 2008)
Applicant: Oscient Pharmaceuticals Corporation

- Noroxin (norfloxacin) Tablets, NDA 19-384/S-052
Submission Date: August 6, 2008 (extension letter dated September 5, 2008)
Applicant: Merck & Co., Inc.

Review Date: September 22, 2008

Deputy Director for Safety: Ozlem Belen, MD, MPH, DDS
Division of Special Pathogens and Transplant Products

Division Director: Renata Albrecht, M.D., Director
Division of Special Pathogens and Transplant Products

DRISK Consultant: Sharon R. Mills, BSN, RN, CCRP
Division of Risk Assessment (DRISK)

DDMAC Consultant: Samuel M. Skariah, Pharm.D.
Division of Drug Marketing and Advertising (DDMAC)

Subject: Review of Fluoroquinolone Class Labeling, including Medication Guide, to update and strengthen the labeling regarding tendinopathy and tendon rupture

Background and Summary:

DSPTP, the Office of Antimicrobial Products (OAP), and the Office of Surveillance and Epidemiology (OSE) reviewed the literature and post marketing adverse event reports in the Adverse Event Reporting System (AERS) for tendinopathy and tendon rupture in association with the use of systemic fluoroquinolones.[1] As a result of these reviews, the FDA sent letters dated July 7, 2008 notifying the fluoroquinolone NDA holders, under Section 505(o)(4) of the Food Drug and Cosmetic Act (FDCA), of the need to include new safety information in the labeling for fluoroquinolone antimicrobial drugs. This information pertained to the risk of tendon-related adverse events with the use of fluoroquinolones, and the new or updated information should specifically be included in the following sections:

- **Boxed Warning**
- **Warnings**
- **Precautions/Information for Patients**
- **Precautions/Geriatric Use**
- **Medication Guide**

[1] Tendon Rupture with the Fluoroquinolones, Maureen Tierney, M.D., Renata Albrecht, M.D., Ed Cox, M.D., MPH, DSPTP/OAP, July 3, 2008
Evelyn R. Farinas, R.Ph., M.G.A., AERS review of Tendon Rupture and Torsade de Pointes; Syed Rizwanuddin Ahmad, M.D., M.P.H., Literature review of fluoroquinolones and risk of tendon injury; Drug Utilization data prepared by Michael Evans, R.Ph., Drug Utilization Specialist; Rosemary Johann-Liang, M.D.; Mark Avigan, M.D. DDRE/OSE, November 23, 2005.

In response to the July 7, 2008 letter, all applicants submitted prior approval labeling supplements with counterproposals to the labeling between August 4, and August 7, 2008. (see supplement numbers, letter dates. The Division reviewed the counterproposals received from all applicants of fluoroquinolone products.

The purpose of this review is to summarize the labeling that will be included in the package inserts of all fluoroquinolones, and to address the labeling proposals to the Medication Guide that were reviewed by the Division, by the Patient Labeling and Education Team in DRISK, and by DDMAC.

The proposed labeling revisions made by the applicants in the package insert for the **Boxed Warning, Warning, Precautions/Information for Patients,** and **Precautions/Geriatric Use** sections were reviewed by DSPTP, and the final wording for these sections, including the location of the informaiton, was provided by fax to the companies on August 25, 2008. The labeling that will be included in the package inserts of all fluoroquinolones is provided below:

1. Addition of a **Boxed Warning**

> **WARNING:**
> **Fluoroquinolones, including TRADENAME, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).**

2. The **WARNINGS/Tendon Effects** subsection of the labeling was renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** section, and updated as follows:

   Tendinopathy and Tendon Rupture: Fluoroquinolones, including TRADENAME, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. TRADENAME should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at

the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

3. The information on tendon adverse reactions in the **PRECAUTIONS/ Information for Patients** subsection of the labeling was moved to the first bullet of the subsection and updated as follows:

• to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue TRADENAME treatment. The risk of serious tendon disorders with fluoroquinolones is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

4. The information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling was moved to the first paragraph of the subsection and updated as follows:

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as TRADENAME. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing TRADENAME to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue TRADENAME and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

The proposed revisions to the Medication Guides were reviewed initially by DSPTP and DRISK, with DRISK providing written reviews summarizing all their recommendations. Where there were differences in labeling recommendations, these were discussed specifically with Sharon R. Mills, BSN, RN, CCRP, and Jodi Duckhorn, M.A., Team Leader in DRISK, and agreement was reached with concurrence obtained via e-mail communication for most of the labeling revisions, and outstanding issues were discussed at the September 16, 2008 meeting. DDMAC was consulted for all fluoroquinolone MedGuides as requested by the DRISK team.

A meeting to discuss the Medication Guides took place on September 16, 2008 between staff from DSPTP (Ozlem Belen, Kristen Miller, Renata Albrecht), the DRISK Team (Sharon R. Mills and Jodi Duckhorn) and the DDMAC Reviewer, Samuel M. Skariah.[2]

[2] The final review and recommendations from Samuel M. Skariah, Pharm.D., DDMAC, were signed in DFS on September 19, 2008.

Recommendations made by various reviewers were discussed, and agreement was reached on the remaining parts of the MedGuide. The Division faxed counterproposals for Medication Guides on September 17, 2008, reflecting the labeling changes that were made by the Division in agreement with DRISK and DDMAC review teams.

Between September 24 and September 26, 2008, the sponsors submitted proposed minor changes to the labeling. The Division reviewed the changes and sent the sponsors the final labeling and Medication Guides on October 2, 2008. The sponsors submitted their concurrence with the final labeling and Medication Guides on October 2, 2008 (Oscient submitted their concurrence on October 3, 2008). The Project Management (PM) labeling review by Kristen Miller, Pharm.D. and Sherry Spriggs dated October 3, 2008 provides a detailed chronology relating to these submissions. The Medication Guide for each product can be found in the October 2, 2008 submissions (October 3, 2008 for Oscient) and the approval letters, dated October 3, 2008.

The review below provides a brief summary of the changes as proposed by DRISK and the DSPTP in the Medication Guide for each drug in this class.

Materials Reviewed include:

1. Current Package Insert (PI) for each of the fluoroquinolones.
2. Medication Guide Consults for each of the respective fluoroquinolone by Patient Labeling and Education Team, Division of Risk Management (DRISK) by Sharon R. Mills, BSN, RN, CCRP and Jodi Duckhorn, M.A. dated August 27 (Cipro®, Avelox®), August 29 (Cipro®XR, Proquin® XR), August 30, (Floxin®), September 1, (Factive®), September 2, (Noroxin®) and September 3, 2008 (Levaquin®).
3. Draft approval letters for each of the respective fluoroquinolone drug product generated by the Review Division (RD), Division of Special Pathogens and Transplant Drug products and reviewed by SRT/OCC.
4. Medication Guide Consults for each of the respective fluoroquinolone by the Division of Drug Marketing, Advertising, and Communications (DDMAC) by Samuel M. Skariah, Pharm.D. dated September 19, 2008 (Avelox®, Cipro®, Factive®, Floxin®, Levaquin®, Noroxin®, Proquin® XR).

Table of Contents……Page

I. CIPRO®…….....6

II. AVELOX……..10

III. PROQUIN XR…….13

IV. LEVAQUIN…….16

V. FLOXIN……20

VI. FACTIVE……..22

VII. NOROXIN…….25

VIII. Medication Guide Discussion Meeting (9/16/2008)……28

I. Drug Name and Application Numbers:

- CIPRO® (ciprofloxacin hydrochloride) Tablets, NDA 19- 537/S-068
- CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-847/S-042
- CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-857/S-049
- CIPRO® (ciprofloxacin) Oral Suspension, NDA 20-780/S-026
- CIPRO® XR (ciprofloxacin extended-release tablets), NDA 21-473/S-024

1. The Applicant proposes a separate Medication Guide (MG) for the IV formulation. MGs are generally for a product, not for a specific formulation and in most cases we recommend one MG. DRISK originally recommended combining the MG for the IV formulation with the MG for the other formulations. Initially, DRISK review team determined that having one MG for all of the formulations is not the best approach for all CIPRO containing products. CIPRO has both adult and pediatric indications and three dosage forms; whereas, CIPRO XR has only adult indications and only one dosage form. In addition, DRISK suggested to include "you and your child" when addressing the patient in the patient labeling since Cipro® had two pediatric indications (complicated Urinary Tract Infections and Pyelonephritis and prevention of inhalational anthrax-post-exposure). Following discussions it was agreed that it is implied that "you" refers to the patient not the MG reader. Therefore, DRISK team agreed with leaving the phrase "you and your child" making it possible to have one MG for all of the formulations including CIPRO XR.

2. The following text was added to section "What is Cipro?": 'Children less than 18 year of age have a higher chance of getting bone, joint, and tendon problems (musculoskeletal) such as pain or swelling while taking CIPRO. CIPRO should not be used as the first choice of antibiotic medicine in children under 18 years of age. CIPRO Tablets, CIPRO Oral Suspension and CIPRO I.V. should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if CIPRO XR is safe and effective in children under 18 years of age.' since pediatric use is not contraindicated in the approved labeling.
DSPTP agrees with this recommendation with minor edits including the addition of tendons into the list of musculoskeletal problems and addition of 'pain and swelling' to expand and define these musculoskeletal problems.

3. Under "What is CIPRO?" the specific list of sites of infection has been replaced with a simple statement. In agreement with the DRISK team and in agreement with DDMAC, it will read as follows: 'CIPRO is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.'

4. The DRISK team suggested the following text in context of breastfeeding (under "What should I tell my healthcare provider before taking CIPRO?"): 'You and your doctor should decide whether you will take CIPRO or breast-feed. You should not do both.'
After internal discussions and informal consultations with the Pediatric and Maternal Health Staff, the Review Division edited this text to read 'You and your doctor should decide whether you will take CIPRO or breastfeed.' The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this decision.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above, in line with the package insert.

5. The PI includes a warning about serious and fatal reactions in patients who take theophylline concurrently with CIPRO. Theophylline is listed under "Tell your healthcare provider about all the medicines you take." in the proposed MG.

6. "Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue CIPRO at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious allergic reactions' in the MG to reflect the PI. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of a hypersensitivity reaction picture rather than drug induced hepatotoxicity. DRISK review team has agreed with this proposal.

'**Yellowing of the skin or eyes.** Stop taking CIPRO and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to CIPRO (a liver problem). '

7. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA. DSPTP modified the wording for paranoia slightly to "feel more

suspicious (paranoia)".

8. Under "What are the possible side effects of CIPRO?" in the context of central nervous effects such as suicide, the DRISK reviewer suggested that reportable signs and symptoms that could precede or lead to suicide or other serious CNS event should be included in the MG so that the patient or family could intervene. As suggested, DSPTP looked in other MGs for examples on how to provide this information and noted that to be consistent with other MG, this section should remain as it is: 'suicidal thought or acts'. DRISK agreed with this wording.

9. The bullet called (b) (4) has been renamed "Low blood sugar (hypoglycemia)." Hypoglycemia with glyburide is mentioned in the drug interactions section of the PI. Hyperglycemia is only mentioned in post-marketing adverse event reports and does not rise to the level of a warning; therefore, DRISK suggested deletion of this language. There is no mention of hypoglycemia with any drug other than glyburide; therefore, the reference to other (b) (4) was deleted by DRISK.
DSPTP agreed with this recommendation.

10. Under "What are the possible side effects of CIPRO?" the following bullet was added in concurrence with the DRISK team and supported by the current labeling 'Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with CIPRO.'

11. Under "What should I avoid while taking CIPRO?" the sun sensitivity language was a discussion point between the DSPTP and DRISK. (b) (4) was found too subjective and vague for the patient labeling. DSPTP proposed that avoiding sunlight totally was not feasible and DRISK and the Review Division has agreed on "try to limit your time in the sun, avoid using tanning beds and sunlamps" in addition to continue including instructions about protective clothing and sunscreen.

12. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.

13. Under "How should I take CIPRO?" the following clarification was made as requested in the DRISK consult:

"If you miss a dose of CIPRO Tablets or Oral Suspension, take it as soon as you remember. Do not take two doses at the same time, and do not take more than two doses in one day.
If you miss a dose of CIPRO XR, take it as soon as you remember. Do not take more than one dose in one day."

14. In the context of anthrax exposure, the following bullet was clarified as per DRISK consult request:
'In most cases, CIPRO Tablets, Oral Suspension and I.V. should not be used in children. CIPRO Tablets, Oral Suspension, I.V. are approved for use in children younger than 18 years old only for anthrax exposure and complicated urinary tract infections.'

15. DRISK commented that language should be added about injection site reaction CIPRO I.V. along with the reportable signs and symptoms including information that discomfort may be lessened by giving the infusion slowly. DSPTP took this suggestion into consideration and reached a conclusion not to add further language regarding injection site reaction in order to avoid additional language which may distract attention from the serious adverse events that this document has set out to communicate. In addition, the I.V. infusion is most likely to take place in an inpatient setting or in the presence of a healthcare provider. DRISK review team has agreed with assessment.

16. In section "What are the possible side effects of CIPRO?" one last bullet was added under the 'serious allergic reactions' bullet ('faint') to make this section of the Medication Guide in parallel with the content of hypersensitivity reactions under the Warnings section of the label.

17. Under "What are the possible side effects of CIPRO?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the labeling.

The following DRISK comments (comments 18 – during PAS approval and 19- during REMS approval process) will be communicated to the Sponsor as proposed by DRISK team.

18. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208.

19. CIPRO Tablets are supplied in bottles of 50, bottles of 100, and in unit dose packages of 100. Unless CIPRO Tablets are distributed in unit of use packaging with the MG enclosed, it is unlikely that patients will receive the MG. The sponsor should state how they intend to ensure that the MG is distributed to all patients who receive a prescription for CIPRO.

II. Drug Name and Application Numbers: Avelox (moxifloxacin hydrochloride) Tablets, NDA 21-085/S-040
Avelox I.V. (moxifloxacin hydrochloride in sodium chloride injection), NDA 21-277/S-034

The following DRISK comments (1st – during PAS approval and 2nd – REMS approval process) will be communicated to the Sponsor as proposed by DRISK team.

1. The Sponsor should comply with all of the Medication Guide Regulations specified in 21 CFR 208.

2. Avelox is supplied in bottles of 30, Unit Dose Pack of 50, and ABC Pack of 5. Unless Avelox is dispensed in unit of use packaging with the MG enclosed, it is unlikely that patients will receive the MG. The sponsor should state how they intend to ensure that the MG is dispensed to all patients who receive a prescription for Avelox.

3. Under "What is AVELOX?" the list of specific sites of infection has been replaced with a simple statement in agreement with the DRISK team and in agreement with DDMAC. It will read as follows: 'AVELOX is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by germs called bacteria in adults 18 years or older.'

4. The DRISK reviewer indicated that Avelox does not have a labeled contraindication for use in children but rather the pediatric use section of the PI says that the safety and effectiveness of Avelox in pediatric patients and adolescents less than 18 years of age has not been established. Therefore the language in the MG should be consistent with the language in the PI. DSPTP agreed with this recommendation and the following text was agreed upon under "What is Avelox?":

   'AVELOX is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain bacteria germs in adults 18 years or older. It is not known if AVELOX is safe and works in people under 18 years of age. Children have a higher chance of getting bone and joint problems (musculoskeletal) while taking fluoroquinolone antibiotic medicines.'

5. Under "How should I take AVELOX?" the following clarification was made as requested in the DRISK consult:

   "If you miss a dose of Avelox, take the dose as soon as you remember. Do not take more than 1 dose of AVELOX in one day."

6. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA.

DSPTP modified the wording for paranoia slightly to "feel more suspicious (paranoia)".

7. The SLR letter directs the sponsor to include this section if needed. (b) (4) are not included in the Warnings or Precautions section of the PI, and were not found to have clinically significant drug interaction with glyburide. DRISK recommended deleting this bullet from the Avelox MG. DSPTP agreed with this recommendation.

8. The DRISK team suggested the following text the context of breastfeeding (under "What should I tell my healthcare provider before taking AVELOX?"): 'You and your doctor should decide whether you will take AVELOX or breast-feed. You should not do both.'
After internal discussions and informal consultations with the Pediatric and Maternal Health Staff the Review Division edited this text to read 'You and your healthcare provider should decide whether you will take AVELOX or breastfeed.' The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this decision.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above, in line with the package insert.

9. The DRISK reviewer pointed out that the information about the use of infusion is (direct infusion or Y infusion and rapid or bolus infusion) directed to healthcare providers and not to patients. Therefore, the following bullet was added under "How should I take AVELOX?" as recommended by the DRISK team:
'AVELOX I.V. is given to you by intravenous (I.V.) infusion into your vein slowly, over 60 minutes, as prescribed by your healthcare provider.'
In addition, under "How should I store AVELOX?" storage instructions for the I.V. formulation were deleted as per DRISK reviewer's recommendation since this formulation will be given by a healthcare provider.

10. Under "What should I avoid while taking AVELOX?" the sun sensitivity language was a discussion point between the DSPTP and DRISK. (b) (4) was found too subjective and vague for the patient labeling. DSPTP proposed that avoiding sunlight totally was not feasible and DRISK and the Review Division has agreed on "try to limit your time in the sun, avoid using tanning beds and sunlamps" in addition to continue including instructions about protective clothing and sunscreen.

11. "Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue CIPRO at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious allergic reactions' in the MG to reflect the PI.
The following wording was added to the MG by the Division in a manner that would make it clear this is a part of hypersensitivity reaction picture rather than drug induced hepatotoxicity. The DRISK review team has agreed with this proposal.

'**Yellowing of the skin or eyes.** Stop taking AVELOX and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to AVELOX (a liver problem).'

12. In section "What are the possible side effects of AVELOX?" one last bullet was added under the 'serious allergic reactions' bullet ('faint') to make this section of the Medication Guide in parallel with the content of hypersensitivity reactions under the Warnings section of the label.

13. Under "What are the possible side effects of AVELOX?" in the context of central nervous effects such as suicide, the DRISK reviewer suggested that reportable signs and symptoms that could precede or lead to suicide or other serious CNS event should be included in the MG so that the patient or family could intervene. As suggested, DSPTP looked in other MGs for examples on how to provide this information and noted that to be consistent with other MG, this section should remain as it is: 'suicidal thought or acts'. DRISK agreed with this wording.

14. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.

15. Under "What are the possible side effects of AVELOX?" a bullet with thethat reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the labeling.

III. Drug Name and Application Numbers: Proquin XR, NDA 21-744/S-008

The following DRISK comments (1st – PAS approval and 2nd – REMS approval process) will be communicated to the Sponsor as proposed by DRISK team.

1. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208.

2. Proquin XR is supplied in bottles of 30, bottles of 50 and Blister Packs of 3. Unless Proquin XR is supplied in unit of use packaging with the MG enclosed, it is highly unlikely that patients will receive the MG. The sponsor should state how they intend to ensure that the MG is distributed to all patients who receive a prescription for Proquin XR.

3. The Proquin XR PI revised by the review division and provided for DRISK review contained a Patient Package Insert (PPI) at the end of the PI. However, the DRISK team was provided a separate Proquin XR proposed MG by DSPTP. This MG along with DRISK suggested revisions will replace the existing PPI at the end of the PI.

4. Under "What is the most important information I should know about Proquin® XR?" the language was revised to be consistent with other MGs for the class. DSPTP has agreed with these recommendations.

5. Under "What is Proquin® XR?" the list of specific site of infection has been replaced with a simple statement by DRISK review team. However, Proquin® XR is approved only for the treatment of uncomplicated urinary tract infections (acute cystitis). It will be important to state this fact, especially because the safety and efficacy of Proquin® XR in treating complicated urinary tract infections have not been demonstrated, this is clearly stated in the current PI. In addition, the current PI also states that 'The safety and effectiveness of Proquin® XR in pediatric patients (less than 18 years of age), have not been established.' This section of the MG will read as follows in order to reflect the current PI:

   'Proquin® XR is a fluoroquinolone antibiotic medicine used to treat simple bladder infections caused by certain germs called bacteria. It is not known if Proquin XR is safe and works in treating any infections other than simple bladder infections. It is also not known if Proquin XR is safe and works in children under 18 years of age. Children have a higher chance of getting bone and joint (musculoskeletal) problems while taking fluoroquinolone antibiotic medicines.' DRISK team has agreed with this recommendation.

6. The DRISK team commented that Proquin® XR is not contraindicated for use in children. The pediatric use section of the PI says that the safety and effectiveness of Proquin® XR in pediatric patients and adolescents less than 18 years of age

has not been established. The MG has been revised to reflect the current PI, in agreement with the DRISK team.

7. The DRISK team suggested the following text in context of breastfeeding (under "What should I tell my healthcare provider before taking Proquin® XR?"): 'You and your doctor should decide whether you will take Proquin® XR or breast-feed. You should not do both.'
After internal discussions and informal consultations with the Pediatric and Maternal Health Staff the Review Division edited this text to read 'You and your healthcare provider should decide whether you will take Proquin® XR or breastfeed.'
The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this decision.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above, in line with the package insert.

8. Under the bullet "Tell your healthcare provider about all the medicines you take" the word 'dietary' was deleted by DRISK. After discussions with the DRISK team, we have agreed to keep this term in this section. An e-mail received from Sharon Mills of OSE on 8.29.08, stated that DRISK team has agreed to add this term back to all fluoroquinolone MGs due to the concern that certain products may be other than a medicine or supplement, and contain certain substances such as metals and fish oils.

9. DSPTP added the wording 'blood thinner' in the context of warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that it is a blood thinner. DRISK has been informed and agreed with this wording.

10. Under "Tell your healthcare provider about all the medicines you take …" following text was added in agreement with the DRISK team (in the context of antiacids, multivitamis, sulcrafate, didanosine):

'Certain medicines may keep PROQUIN XR from working correctly. Take Proquin® XR at least 4 hours before or 2 hours after taking these products.'

11. The PI includes a warning about serious and fatal reactions with patients who take theophylline concurrently with Proquin XR. Theophylline is listed under "Tell your healthcare provider about all the medicines you take." in the proposed MG.

12. Under "How should I take Proquin® XR?" the following clarification was made as requested in the DRISK consult:

'If you miss a dose of Proquin XR, take it as soon as you remember. Do not take more than one Proquin® XR tablet a day, even if you miss a dose.'

13. Under "What should I avoid while taking Proquin® XR?" the sun sensitivity language was a discussion point between the DSPTP and DRISK (b) (4) was found too subjective and vague for the patient labeling. DSPTP proposed that avoiding sunlight totally was not feasible and DRISK and the Review Division has agreed on "try to limit your time in the sun, avoid using tanning beds and sunlamps" in addition to continue including instructions about protective clothing and sunscreen.

14. Under "What are the possible side effects of Proquin XR?" in the context of central nervous effects such as suicide, the DRISK reviewer suggested that reportable signs and symptoms that could precede or lead to suicide or other serious CNS event should be included in the MG so that the patient or family could intervene. As suggested, DSPTP looked in other MGs for examples on how to provide this information and noted that to be consistent with other MG, this section should remain as it is: 'suicidal thought or acts'. DRISK agreed with this wording.

15. In the section "What are the possible side effects of Proquin XR?":

a. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA. DSPTP modified the wording for paranoia slightly to "feel more suspicious (paranoia)".

b. "Liver problems" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue Proquin XR at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious allergic reactions' in the MG to reflect the PI.
"Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of hypersensitivity reaction picture rather than drug induced hepatotoxicity. The DRISK review team has agreed with this proposal.

'**Yellowing of the skin or eyes.** Stop taking Proquin XR and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to Proquin® XR (a liver problem).'

c. In the bullet named (b) (4) hypoglycemia with glyburide is mentioned in the drug interactions section of the PI. Hyperglycemia is only mentioned in postmarketing adverse event reports and was assessed as not rising to the level of a warning; therefore, DRISK recommended deleting this language. There is no mention of hypoglycemia with any drug other than glyburide DRISK team suggested deleting reference to other oral antidiabetes agents and insulin. DSPTP agreed with these recommendations.

d. Under "What are the possible side effects of Proquin® XR?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the labeling.

IV. Drug Name and Application Numbers:

Levaquin® (levofloxacin) Tablets, NDA 20-634/S-052
Levaquin® (levofloxacin) Oral Solution, NDA 21-721/S-020
Levaquin® (levofloxacin) Injection and Levaquin® (levofloxacin in 5% dextrose) Injection, NDA 20-635/S-057

Application Type/Number:

The following DRISK comments (1st – during PAS approval and 2nd – during REMS approval process) will be communicated to the Sponsor as proposed by DRISK team.

1. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208.

2. The sponsor should state how they intend to ensure that the MG is distributed to all patients who receive a prescription for Levaquin.
   Levaquin is supplied in:
   - **a.** 250 mg Tablets: bottles of 50 and unit-dose /100 tablets
   - **b.** 500 mg Tablets: bottles of 50 and unit-dose/100 tablets
   - **c.** 750 mg Tablets: bottles of 20, unit dose/100 tablets
   - **d.** Levaquin Oral Solution: 16 oz. multi-use bottle.
   - **e.** Levaquin Injection: single-use vials
   - **f.** Levaquin Injection Premix: single-use premixed solution in flexible containers.

3. The DRISK team noted that PI for Levaquin is in the PLR format; whereas the labeling for the other fluoroquinolone products remain in the older labeling format. The difference in labeling formats has in some cases required certain information be placed in different areas of the MG than in other fluoroquinolone products' MG. This may give the appearance that some information carries lesser importance. DSPTP has taken a close look at these changes specifically in the Levaquin MG to ensure that class safety information is addressed in it consistently, as appropriate.

4. The pediatric information will be included in the section "What is LEVAQUIN?" as recommended by the DRISK team and in agreement with DDMAC this section will read as follows in line with the current PI:
'LEVAQUIN® is a fluoroquinolone antibiotic medicine used in adults, 18 years or older, to treat certain infections caused by certain bacteria germs called bacteria.

In children 6 months and older who have breathed the anthrax bacteria germ:

- LEVAQUIN is used to prevent anthrax disease (inhalation anthrax).
- It is not known if it is safe to use LEVAQUIN in children for more than 14 days.

It is not known if LEVAQUIN is safe and works in children under the age of 6 months. Children have a higher chance of getting bone, joint, or tendon problems (musculoskeletal) such as pain or swelling while taking LEVAQUIN®.'

5. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.

6. Under "Tell your healthcare provider about all the medicines you take …" following text was added in agreement with the DRISK team (in the context of antiacids, multivitamins, sulcrafate, and didanosine):

'Certain medicines may keep LEVAQUIN from working correctly. Take LEVAQUIN® Tablets or ORAL Solution either 2 hours before or 2 hours after taking these products:'

7. Under "How should I take LEVAQUIN®?" the following clarification was made as requested in the DRISK consult.

'If you miss a dose of LEVAQUIN®, take it as soon as you remember. Do not take more than one dose in one day.'

8. In the section "How should I take Levaquin?" DRISK consultant has added proposed language to the 4th bullet in "If you have been prescribed LEVAQUIN® after being exposed to anthrax." DRISK noted that the PI for Levaquin has language that is not included in the Cipro PI regarding use for

longer than 28 days in adult and for longer than 14 days in children 6 months of age and older. DRISK reviewer brought attention to this disparity. DSPTP is aware of this difference in the respective labels and the PI and the clinical trial data leading to this difference supports this.
This information has been added to the MG based on the information in section 14.9 Inhalational Anthrax (post-exposure).

9. Section 8, Use in Specific Populations, subsection 8.3 in the PI states that "Based on data on other fluoroquinolones and very limited data on Levaquin, it can be presumed that levofloxacin will be excreted in human milk."
The DRISK team suggested the following text in context of breastfeeding (under "What is the most important information I should know about LEVAQUIN®?"):

'Levaquin® is thought to pass into breast milk. Talk to your healthcare provider about whether you will take Levaquin® or breast-feed."

After internal discussions and informal consultations with the Pediatric and Maternal Health Staff the Review Division edited this text to read 'LEVAQUIN® is thought to pass into breast milk. You and your healthcare provider should decide whether you will take Levaquin or breastfeed.' The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this decision.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above, inline with the package insert.

10. In the section, "What should I avoid while taking Levaquin?" the bullet concerning exposure to sunlight, sunlamps, and tanning beds, sunscreen is not listed as in the other fluoroquinolone PIs. The DRISK reviewer proposed deleting information about sunscreen from the MG. The Levaquin PI directs patients to wear clothing to protect their skin and to talk with their healthcare provider about other sun protection measures. DSPTP reviewed this information, and will keep this section in line with the other MG. Following discussions an agreement was reached to keep this wording consistent with the other MG for this class (fluoroquionolones).
In addition, "Avoid sunlamps, tanning beds, and try to limit your time in the sun." is the language used in all the MGs fluoroquinolone class antibiotics in agreement with DRISK team.

11. Under "What are the possible side effects of LEVAQUIN®?" in the context of central nervous effects such as suicide, the DRISK reviewer suggested that

reportable signs and symptoms that could precede or lead to suicide or other serious CNS event should be included in the MG so that the patient or family could intervene. As suggested, DSPTP looked in other MGs for examples on how to provide this information and noted that to be consistent with other MG, this section should remain as it is: 'suicidal thought or acts'. DRISK agreed with this wording.

12. Under "What are the possible side effects of LEVAQUIN®?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the labeling.

13. In the section, "What are the possible side effects of LEVAQUIN®?":

a. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA. DSPTP modified the wording for paranoia slightly to "feel more suspicious (paranoia)".

b. Liver language has been added because of the information under Hypersensitivity Reactions in subsection 5.3 of Warnings and Precautions section 5 of the PI to discontinue Levaquin at the first appearance of jaundice. The DRISK team suggested adding this information to subsection 17.3 of section 17 Patient Counseling Information in the PI for Levaquin.
"Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of a hypersensitivity reaction picture rather than drug induced hepatotoxicity. DRISK review team has agreed with this proposal.

'**Yellowing of the skin or eyes.** Stop taking LEVAQUIN® and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to LEVAQUIN® (a liver problem).'

c. The DRISK team added information about low blood pressure in patients who receive Levaquin by the IV route if given too fast, and provided reportable symptoms. DSPTP agrees with this recommendation.

d. For consistency, we have used the same language regarding false-positive urine screening for opiates, which was used in the DRISK review of the FLOXIN MG. DSPTP agrees with this recommendation.

V. Drug Name and Application Numbers: Floxin Tablets (Ofloxacin Tablets), NDA 19-735/S-059

The following DRISK comments (1st – during PAS approval and 2nd – during REMS approval process) will be communicated to the Sponsor in the approval letter as proposed by DRISK team.

1. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208.

2. The DRISK reviewer noted that FLOXIN does not have a labeled contraindication for use in children. The pediatric use section of the PI says that the safety and effectiveness of FLOXIN in pediatric patients and adolescents less than 18 years of age has not been established. There is no language in the PI stating that use of FLOXIN in patients below the age of 18 is not recommended. The language in the MG must be consistent with the language in the PI. DSPTP followed this recommendation.
   In this section, "What is Floxin®?" the text will read 'FLOXIN® is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain germs called bacteria in adults. It is not known if FLOXIN® is safe and works in people under 18 years of age. Children have a higher chance of getting bone and joint problems (musculoskeletal) while taking fluoroquinolone antibiotic medicines.' in agreement with the DRISK team.

3. In the section "What should I tell my healthcare provider before taking FLOXIN®?" the bullet (b) (4) was deleted; this is not in the other fluoroquinolone MG. DSPTP agreed with this recommendation. In the same section, additional information was added in the context of 'kidney problems. You may need a lower dose of FLOXIN if you have certain kidney problems.' Finally, 'liver problems' was added as a bullet.

4. The DRISK team suggested the following text in context of breastfeeding (under "What should I tell my healthcare provider before taking FLOXIN®?"):
   'FLOXIN® passes into breast milk. You should talk to your doctor about whether you will take FLOXIN or breast feed. You should not do both.'

   After internal discussions and informal consultations with the Pediatric and Maternal Health Staff the Review Division edited this text to read 'FLOXIN® is thought to pass into breast milk. You and your healthcare provider should decide whether you will take FLOXIN® or breastfeed.' The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this

decision, in line with the package insert.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above.

5. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.

6. In the section, "Tell your healthcare provider about all the medicines you take," following text was added in agreement with the DRISK team (in the context of antiacids, multivitamins, dietary supplements, sulcrafate, and diadanosine):

'Certain medicines may keep FLOXIN from working correctly. Take FLOXIN either 2 hours before or 2 hours after taking these products:'

7. Under "How should I take FLOXIN?" the following clarification was made as recommended in the DRISK consult:

'If you miss a dose of FLOXIN, take it as soon as you remember. Do not take two doses of FLOXIN at the same time. Do not take more than two doses in one day.'
'If you take too much, call your healthcare provider or get medical help immediately.'

8. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA. DSPTP modified slightly to use the term "feel more suspicious (paranoia)".

9. Under "What are the possible side effects of FLOXIN?" in the context of central nervous effects such as suicide, the DRISK reviewer suggested that reportable signs and symptoms that could precede or lead to suicide or other serious CNS event should be included in the MG so that the patient or family could intervene. As suggested, DSPTP looked in other MGs for examples on how to provide this information and noted that to be consistent with other MG, this section should remain as it is: 'suicidal thought or acts'. DRISK agreed with this wording.

10. "Liver problems" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue Proquin XR at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious allergic reactions' in the MG to reflect the PI. "Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of a hypersensitivity reaction picture rather than drug induced hepatotoxicity. DRISK review team has agreed with this proposal.

'**Yellowing of the skin or eyes.** Stop taking FLOXIN® and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to FLOXIN® (a liver problem).'

11. Under "What are the possible side effects of FLOXIN®?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be the similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the label.

Serious heart rhythm changes (QTc prolongation and torsade de pointes) bullet moved up to follow skin rash to be consistent with placement of information in other Fluoroquinolone MGs as per DRISK team consult.

12. The Peripheral neuropathy bullet was moved to follow the intestinal infection bullet (Pseudomembranous colitis to be consistent with the location in the MG for other fluoroquinolone products as per the DRISK team recommendation.

13. For consistency, the same language regarding false-positive urine screening for opiates, which was used in DRISK review of the LEVAQUIN® MG based on the current PI. The paragraph about possible false-positive urine screening results for opiates has been moved to the section "What are the possible side effects of FLOXIN?" This is a potential interaction with a laboratory test which can be significant to patients. DSPTP agrees with this recommendation.

VI. Drug Name and Application Numbers:

FACTIVE (gemifloxacin mesylate) Tablets, NDA 21-158/S-012

The following DRISK comments (1st – during PAS approval and 2nd – during REMS approval process) will be conveyed to the Sponsor in the approval letter as proposed by DRISK team.

1. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208.

2. FACTIVE is supplied in unit of use packaging. This is the optimal packaging configuration in which to ensure that the MG is enclosed with the product and is distributed to patients. The sponsor should verify that they intend to enclose the MG in the FACTIVE packaging.

3. The FACTIVE PI revised by the review division contains patient labeling at the end of it, called "Patient Information." The PPI should be replaced with the Medication Guide once it is approved. DSPTP agrees with this recommendation.

4. In the section "What is FACTIVE?"

a. The DRISK reviewer pointed out that FACTIVE does not have a labeled contraindication for use in children and the language here should be consistent with the current PI. The text in this section will read as follows in agreement with the DRISK team:

'FACTIVE is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain germs called bacteria. It is not known if FACTIVE is safe and works in children under 18 years of age. Children have a higher chance of getting bone and joint (musculoskeletal) problems while taking FACTIVE.'

b. The pediatric language has been moved from the section "Who should not take FACTIVE?" to this section following discussions with the DRISK team. The comment (b) (4) have been deleted to make the MG consistent with the current PI. DSPTP has agreed with this recommendation.

5. In the section, "What should I avoid while taking FACTIVE?" the bullet concerning exposure to sunlight, sunlamps, and tanning beds will read as: 'Avoid sunlamps and tanning beds, and try to limit your time in the sun." in agreement with the DRISK review team.

6. In the section "How should I take FACTIVE?' it was noted that FACTIVE PI tells the patients that "FACTIVE can be taken with or without food and should be swallowed whole with a liberal amount of liquid." This issue was addressed as recommended and this section will read as in parallel with the PI:
' FACTIVE can be taken with or without food. Swallow FACTIVE whole, and drink plenty of fluid with it…'

7. In the section, "What are the possible side effects of FACTIVE?"

a. DRISK defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA. DSPTP modified the wording for paranoia slightly to "feel more suspicious (paranoia)".

b. "Liver problems" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue Proquin XR at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious

allergic reactions' in the MG to reflect the PI.
"Yellowing of the skin or eyes" has been added to address jaundice under the bullet for serious allergic reactions. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of a hypersensitivity reaction picture rather than drug induced hepatotoxicity. The DRISK review team has agreed with this proposal.

'Yellowing of the skin or eyes. Stop taking FACTIVE and call your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to FACTIVE (a liver problem).'

c. The sponsor deleted the Fluoroquinolone MG template bullet (b) (4) from the MG section "What are the possible side effects of FACTIVE. It is noted that no drug interactions are listed in the PI for FACTIVE and oral antidiabetes drugs or insulin. The PI lists hyperglycemia in less than 1% of patients. DSPTP will keep this section in line with the PI for each product in agreement with the DRISK review team; therefore deletion of (b) (4) from this section will be acceptable.

8. Under the section, "What should I tell my healthcare provider before taking FACTIVE?" in the context of medical conditions that needs to be discussed with the healthcare provider will include:

a. a bullet for low blood potassium (hypokalemia) or magnesium (hypomagnesemia) based on the PI.

b. a bullet for patients with slow heart beat (bradycardia) based on the PI.

c. a bullet for broader term of seizures rather than epilepsy as recommended by DRISK team.

d. 'You may need lower dose of FACTIVE. Was added in the context of kidney problems in this section.

e. (b) (4) was deleted as recommended by the DRISK review team. Other fluoroquinolone MGs do not include this bullet.

9. The DRISK team suggested the following text in context of breastfeeding (under "What should I tell my healthcare provider before taking FACTIVE?"):
'It is not known if FACTIVE passes into breast milk. Talk to your healthcare provider about the best way to feed your baby while taking FACTIVE.'

After internal discussions and informal consultations with the Pediatric and Maternal Health Staff the Review Division edited this text to read 'It is not known

if FACTIVE passes into breast milk. You should not talk to your doctor about whether you will take FLOXIN® or breast-feed. ' The fluoroquinolones do appear to get into breast milk, but the percentage of the blood level that gets in is unknown. There is no contraindication in the current labeling and that is being proposed by saying that you should not do both. The most important message is that the patient should not do both without consulting her healthcare provider who can take the benefits of breastfeeding and the risk of fluoroquinolone exposure via breastfeeding that exists for the infant into consideration when making this decision.
During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between the DRISK and the Division) on September 16, 2008, an agreement was reached to keep the wording as stated above.

10. In the section, "Tell your healthcare provider about all the medicines you take," following text was added in agreement with the DRISK team:

'Take Factive at least 2 hours before you take sulcrafate (Carafate).'
'Take FACTIVE either 2 hours before or 3 hours after taking these products:' with respect to antiacids, multivitamins and didanosine.

11. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.
In addition, the following bullet was added to this section as recommended by DRISK reviewer based on the PI "probenecid (Probalan, Col-Probenecid)'.

12. Under the section, "How should I take FACTIVE?" the following section added: 'Swallow FACTIVE whole, and drink plenty of fluids with it. Do not chew FACTIVE. Tell your healthcare provider if you are not able to swallow FACTIVE whole. You will need to take a different antibiotic medicine.' In agreement with DRISK review team.

13. Under "What are the possible side effects of FACTIVE?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be the similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the labeling.

VII. Drug Name and Application Numbers: Noroxin (norfloxacin) Tablets, NDA 19-384/S-052

The following DRISK comments (1st – during PAS approval and 2nd – during REMS approval process) will be communicated to the Sponsor in the approval letter as proposed

by DRISK team.

1. The sponsor must comply with all of the MG regulations as specified in 21 CFR 208.

2. NOROXIN is supplied in bottles of 100 as well as unit of use bottles of 20. Unless all NOROXIN is dispensed in unit of use packaging with the MG enclosed, it is unlikely that patients will receive the MG. The sponsor should state how they intend to ensure that all patients who fill a prescription for NOROXIN will receive a MG.

3. Pediatric language has been moved from the section "Who should not take NOROXIN?" to section "What is Noroxin?" In addition, the comment 'NOROXIN is not recommended for use in children in order to make the MG consistent with the PI as per recommendation of the DRISK team. This section now reads as follows:

   'NOROXIN is a fluoroquinolone antibiotic medicine used in adults to treat certain infections caused by certain germs called bacteria. It is not known if NOROXIN is safe and works in children under 18 years of age. Children have a higher chance of getting bone and joint (musculoskeletal) problems while taking NOROXIN.'

4. In the section "How should I take NOROXIN?" the instruction telling the patients to take NOROXIN with a "large glass of water" was taken out as the tem "large was found too subjective by the DRISK reviewer. DSPTP agrees with this. As in other fluoroquinolone PIs, the NOROXIN PI tells patients to "drink fluid liberally". This section will include a bullet "Take a NOROXIN with a glass of water." And another one "Drink plenty of fluids while taking NOROXIN." In line with the PI.

5. In the section, "What are the possible side effects of NOROXIN?":

   a. DRISK defined the terms "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA.

   b. (b) (4) are not included in the NOROXIN PI and therefore have been deleted from the respective MG as recommended by the DRISK reviewer.

   c. "Liver problems" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue NOROXIN at the first appearance of jaundice. The DRISK reviewer suggested that this information should be added under 'serious allergic reactions' in the MG to reflect the PI.
   "Yellowing of the skin or eyes" has been added to address jaundice under

the bullet for serious allergic reactions. The following wording was added to the MG by the Division in a manner that would make it clear this is a part of hypersensitivity reaction picture rather than drug induced hepatotoxicity. The DRISK review team has agreed with this proposal.

d. The PI for NOROXIN includes information about myasthenia gravis in the Precautions section of the labeling. The labeling for other fluoroquinolones do not single out this side effect in Warning and Precautions. 'Worsening of myasthenia gravis symptoms.' were added under this section in line with the PI.

e. The following text was added based on the PI as recommended by the DRISK review team: 'Low blood sugar (hypoglycemia). People taking NOROXIN and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe.'

6. Under the section "Who should not take NOROXIN?" one bullet will be 'have ever had a severe allergic reaction to antibiotic known as a fluoroquinolone, are allergic to any of the ingredients in NOROXIN. See the list of ingredients in NOROXIN at the end of this medication Guide.' The DRISK reviewer recommended that the Review Division should check the language in all of the fluoroquinolone PIs and make the allergy language in the MGs the same, as appropriate. DSPTP followed this recommendation.

7. Under the section "Who should not take NOROXIN?" a second bullet will include 'have had tendinitis or tendon rupture with use of NOROXIN or another fluoroquinolone antibiotic.', in line with the PI.

8. Under the section, "What should I tell my healthcare provider before taking NOROXIN?" in the context of medicines that the patient takes, following clarification was made as per DRISK recommendation: 'certain medicines may keep NOROXIN from working correctly. Take NOROXIN either 2 hours before or 2 hours after taking these products" in the context o f antacids, multivitamins, sulcrafate and didanosine.

9. Under the section, "What should I tell my healthcare provider before taking NOROXIN?", the following text was added as per DRISK recommendations based on the PI: 'You should not take the medicine nitrofuantoin (furadantin, macordantin, macrobid) while taking NOROXIN.

10. DSPTP added the wording 'blood thinner' to describe warfarin, Coumadin, Jantoven under "Tell your healthcare provider about all the medicines you take …" for an easy reminder for patients who take these drugs but do not realize that they are a blood thinner. DRISK agreed with this wording.

11. An instruction telling patients what to do in case of an overdose was added into the section "How should I take NOROXIN?" as per DRISK review team: 'If you take too much, call your healthcare provider or get medical help immediately.'

12. In the section, "What should I avoid while taking NOROXIN?" the bullet concerning exposure to sunlight, sunlamps, and tanning beds will read as: 'Avoid sunlamps and tanning beds, and try to limit your time in the sun." in agreement with the DRISK review team.

14. Under "What are the possible side effects of NOROXIN?" a bullet that reads 'serious heart rhythm changes (QTc prolongation and torsade de pointes)' was added in order to make Medication Guide consistent with the product labeling. This language will be the similar in all MG of this class. A reference to increased chance of QTc prolongation in the elderly population was made to reflect previous labeling changes in the Geriatric Use section of the label.

15. During the follow-up meeting to discuss outstanding issues in the MG for fluoroquinolones (between DRISK and the Division) on September 16, 2008, the following text was agreed upon in the context of breastfeeding (under "What should I tell my healthcare provider before taking FACTIVE?") to keep all MG consistent:
'It is not known if NOROXIN passes into breast milk. You and your healthcare provider should decide whether you will take NOROXIN or breast feed.'

VIII. Medication Guide Discussion Meeting on September 16, 2008 between DSPTP Review Division, DRISK Team (Sharon R. Mills, BSN, RN, CCRP, and Jodi Duckhorn, M.A.,) and DDMAC Reviewer Samuel M. Skariah, Pharm.D.

During this meeting outstanding issues surrounding the respective fluoroquinolone medication guides were discussed and agreement was reached. These discussion points apply to each fluoroquinolone Medication Guide summarized in this document.

- 'TRADENAME is a fluoroquinolone antibiotic medicine used to treat certain types of infections caused by certain germs called bacteria…' will be under "What is TRADENAME?"
- The sites of infection (lung, sinus, abdomen, skin etc.) will not be included in the respective MG except for Proquin XR. The inclusion of these sited increase the grade reading level which may decrease comprehension by the reader. Proquin XR will include information that it is used to treat simple bladder infections specifically because it does not have any other indication and it is not known if Proquin XR is safe and effective in treating other infections.
- The term "swelling of the tendon (tendinitis)" in addition to tendon rupture was added in order to more appropriately describe the new warning.
- 'Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles)' was clarified for some readers may not be able to comprehend what is meant by the term "Achilles".

- 'Swelling of the tendon (tendonitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors' was added for more clarification following DDMAC recommendations.
- 'Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported.' was added as per DDMAC recommendation.
- DDMAC recommended that adding an example of an NSAID, antipsychotic medicine, a trycyclic antidepressant, and a "a medicine to control your heart rate or rhythm"; the DRISK review commented that if we add one example, the MG will have to include all of the drugs referred in these classes which will not be feasible. Therefore an agreement was reached and this section will not change.
- DSPTP noted that the MG now approached 9 pages in length and may exceed the targeted reading level. The DRISK review team stated this issue was under discussion.
- DRISK confirmed that the MedWatch 1-800— number statement, at the end of the MG had to be written verbatim as in the rule.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ozlem Belen
10/3/2008 09:43:39 PM
MEDICAL OFFICER

Renata Albrecht
10/3/2008 09:53:53 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 27, 2008
To:	Renata Albrecht, M.D., Director **Division of Special Pathogens and Transplant Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Medication Guide)
Drug Name and Application Numbers	• CIPRO® (ciprofloxacin hydrochloride) Tablets, NDA 19-537/S-068 • CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-847/S-042 • CIPRO® IV (ciprofloxacin) For Intravenous Infusion, NDA 19-857/S-049 • CIPRO® (ciprofloxacin) Oral Suspension, NDA 20-780/S-026
Applicant/sponsor:	Bayer Pharmaceuticals Inc.
OSE RCM #:	2008-1295

1 INTRODUCTION

Title IX, Subtitle A., Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes (section 505 (o) (4) of the FDCA) and require the submission of a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1(a)(2) for an approved drug based upon new safety information that becomes available after the approval of the drug.

The current Professional Information for all Cipro products contains class labeling for all fluoroquinolones regarding the risk of tendon-related adverse events. On July 7, 20008, the Review Division notified Bayer Pharmaceuticals Corporation that the current labeling for all Cipro® containing products do not adequately warn healthcare providers and patients about the increased risk of tendon rupture. The sponsor was advised of required safety labeling changes, which includes a boxed warning about tendon effects, including tendon ruptures. In addition, the sponsor was informed that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. FDA has determined in accordance with 21 CFR 208.1, that Cipro® containing products pose a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use, and FDA has determined that:

> "the drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product."

In addition to the Medication Guide the REMS includes a Timetable for assessment.

The review division provided the sponsor with a proposed draft Medication Guide developed in collaboration with the Patient Labeling and Education Team. See our review of the Proposed Class Medication Guide Template for Fluoroquinolone Antibiotics, dated April 25, 2008.

On August 5, 2008, the sponsor submitted Prior Approval Labeling Supplements to multiple NDAs for Cipro containing products. For NDA 19-537/S-068 and NDA 20-780/S-026, cross-referencing to NDA 19-537, submitted labeling includes common draft Professional Information and a common proposed Medication Guide (MG). The sponsor also submitted a Prior approval supplement, sNDA 19-847 for Cipro (ciprofloxacin) I.V. solution, including draft Professional Information and a separate proposed MG for the I.V. formulation. NDA 19-857 cross-references NDA 19-847 and shares its proposed draft Professional Information and proposed MG.

The review division requested that the Patient Labeling and Education Team review the sponsor's proposed MGs. This review is written in response to that request.

2 MATERIAL REVIEWED

- DRAFT Professional Information for: Cipro (ciprofloxacin hydrochloride tablets) and Cipro (ciprofloxacin) Oral Suspension, submitted July 7, 2008 and further revised by the review division on August 12, 2008.
- DRAFT Professional Information for: Cipro I.V.(ciprofloxacin) for Intravenous Infusion, submitted July 7, 2008 and further revised by the review division on August 12, 2008.

- DRAFT Medication Guide (MG) for all the above formulations, submitted July 7, 2008 as two separate MGs, and further revised by the review division on August 12, 2008 and combined into one MG for Cipro.

3 DISCUSSION

The purpose of Medication Guides (MG) is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor for CIPRO Tablets and CIPRO Oral Suspension has a Flesch Kinkaid grade level of 9.3, and a Flesch Reading Ease score of 53.4 %. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG which includes information for the CIPRO I.V. formulation has a Flesch Kinkaid grade level of 8.4 and a Flesch Reading Ease score of 58.7%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- made the MG consistent with the PI,
- made the MG consistent with the Fluoroquinolone antibiotic class MG template developed by the RD in collaboration with the Patient Labeling and Education Team
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The sponsor proposes a separate MG for the IV formulation. Medication Guides (MGs) are generally for a product, not for a specific formulation and in most cases we recommend one MG. We originally recommended combining the MG for the IV formulation with the MG for the other formulations. However, after reviewing all of the material and discussing this with Dr. Belen, we have determined that having one MG for all of the formulations is not the best approach for all CIPRO containing

products. CIPRO has both adult and pediatric indications and three dose forms; whereas, CIPRO XR has only adult indications and only one dose form. One MG will contain all of the information pertaining to CIPRO for the tablet, oral suspension and I.V. dose forms. The second MG will contain all of the information pertaining to CIPRO XR (ciprofloxacin extended-release tablets). The CIPRO XR MG is being provided in a separate review to the Review Division under sNDA 21-473/S-024.

2. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208. In particular, the carton and container labels must comply with 21 CFR208.24 (a) (2) (d). To our knowledge these labels have not yet been submitted to the Agency for review.
3. CIPRO Tablets are supplied in bottles of 50, bottles of 100, and in unit dose packages of 100. Unless CIPRO Tablets are distributed in unit of use packaging with the MG enclosed, it is unlikely that patients will receive the MG. The sponsor should state how they intend to ensure that the MG is distributed to all patients who receive a prescription for CIPRO.
4. The PI includes a bolded warning about serious and fatal reactions with patients who take theophylline concurrently with CIPRO. The review division should consider whether CIPRO should be contraindicated in patients taking theophylline. If this must be addressed at a later time, the review division should consider appropriate language to convey this risk to patients.
5. In the section, "What are the possible side effects of CIPRO?":
    - We defined the terms "paranoia" and "hallucinations" with simple language taken from the Geodon Patient Package Insert currently posted on Drugs @ FDA.
    - "Liver problems" has been added to address jaundice under the bullet for serious allergic reactions. Information listed under Hypersensitivity Reactions in the Warnings section of the PI provides the instruction to discontinue CIPRO at the first appearance of jaundice. Consider adding this information to the Information for Patients subsection of the Precautions section of the PI.
    - The bullet called (b) (4) has been renamed "Low blood sugar (hypoglycemia)." Hypoglycemia with glyburide is mentioned in the drug interactions section of the PI. Hyperglycemia is only mentioned in post-marketing adverse event reports and does not rise to the level of a warning; therefore, we deleted this language. There is no mention of hypoglycemia with any drug other than glyburide; therefore, (b) (4) The review division should clarify and update the PI as appropriate if there is evidence of hypoglycemia with other drugs. The language in the MG must be consistent with the language in the PI.
    - Language should be added about injection site reaction for CIPRO I.V. along with reportable signs and symptoms. Include information that discomfort may be lessened by giving the infusion slowly.

Please let us know if you have any questions.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Mills
8/27/2008 06:24:13 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
8/27/2008 08:31:35 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2008

To: Janet Herrington, Ph.D.	**From:** Kristen Miller, Pharm.D.
Company: Bayer Pharmaceuticals Corp.	Division of Special Pathogen and Transplant Products
Email Address: janet.herrington.b@bayer.com	**Fax Number:** 301-796-9882
Phone Number:	**Phone Number:** 301-796-0762

Subject: Updated wording for SLR submissions

Total no. of pages including cover:

Comments: Concur:
Ozlem Belen, M.D. Deputy Director of Safety

Document to be mailed: ☐ YES ☑ NO

Please refer to your supplemental new drug applications (NDA) for CIPRO® (ciprofloxacin), NDAs 19-537/S-068, 19-847/S-042, 19-857/S-049, 20-780/S-026, and 21-473/S-024. Please also refer to our July 7, 2008 supplement request to update the labeling with regard to tendinitis and tendon rupture, and our August 26, 2008 communication with preliminary modifications to the proposed labeling.

In response to the August 26, 2008 communication, we received counterproposals from a few sponsors of fluoroquinolone products. We have also received feedback from the Office of Surveillance and Epidemiology and the Division of Drug Marketing, Advertising and Communication on the Medication Guides. We have reviewed the counterproposals and the consult reviews and have made a few additional modifications to the wording from our original request (and from the August 26, 2008 communication). The Agency is preparing to approve the labeling changes and Medication Guide below (additions are noted by underline and deletions are noted by ~~strikethrough~~ replacing "CIPRO" with "CIPRO XR" where appropriate in the Cipro XR® labeling). The changes below are based on the current approved labeling. Please note that the information regarding tendon effects was moved to the beginning of each respective subsection.

Please submit to your NDAs a formal submission with the below labeling changes incorporated (Word or pdf is sufficient) by September 25, 2008.

We are providing this information via email for your convenience. Please contact me at 301-796-1600 if you have any questions.

_____

Kristen Miller, Pharm.D.
Safety Regulatory Project Manager

1. A **Boxed Warning** with bolded font and enclosed in a black box was added to the beginning of the labeling as follows:

> **WARNING:**
> **Fluoroquinolones, including CIPRO®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).**

2. The **WARNINGS/Tendon Effects** subsection of the labeling was renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** section, and updated as follows:

   Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also

been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

~~**Tendon Effects:** Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Ciprofloxacin 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 tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.~~

3. The information on tendon adverse reactions in the **PRECAUTIONS/ Information for Patients** subsection of the labeling was moved to the first bullet of the subsection and updated as follows:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO® treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- ~~to discontinue CIPRO treatment, rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids.~~

4. The information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling was moved to the first paragraph of the subsection and updated as follows:

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after

fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

~~Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.~~

5. The Patient Package Insert for CIPRO Tablets, Oral Suspension, I.V., and CIPRO XR was replaced with a Medication Guide as follows:

MEDICATION GUIDE

CIPRO® *(Sip-row)*
(ciprofloxacin hydrochloride)
TABLETS

CIPRO® *(Sip-row)*
(ciprofloxacin)
ORAL SUSPENSION

CIPRO® XR *(Sip-row)*
(ciprofloxacin extended-release tablets)

CIPRO® I.V. *(Sip-row)*
(ciprofloxacin)
For Intravenous Infusion

Read the Medication Guide that comes with CIPRO® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CIPRO?

CIPRO is an antibiotic called a fluoroquinolone. CIPRO can cause side effects that may be serious or even cause death. If you have any of the following serious side effects, get medical help right away, and talk with your healthcare provider about whether you should continue taking CIPRO.

- **Tendon rupture or swelling of the tendon (tendinitits)**
- Tendons are tough cords of tissue that connect muscles to bones.
- Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including CIPRO. The risk of getting tendon problems is higher if you:
  - are over 60 years of age
  - take steroids (corticosteroids)
  - have had a kidney, heart, or lung transplant
- Swelling of the tendon (tendinitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
- Other reasons for tendon ruptures can include:
  - physical activity or exercise
  - kidney failure
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
- Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking CIPRO until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of CIPRO. You may need a different antibiotic that does not have a fluoroquinolone to treat your infection.
- Tendon rupture can happen while you are taking or after you have finished taking CIPRO. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- Get medical help right away if you have any of the following signs or symptoms of a tendon rupture:
  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area
  - unable to move the affected area or bear weight
- See the section "**What are the possible side effects of CIPRO**" for more information about side effects.

What is CIPRO?

CIPRO is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.

Children less than 18 year of age have a higher chance of getting bone, joint, and tendon (musculoskeletal) problems such as pain or swelling while taking CIPRO. CIPRO should not be used as the first choice of antibiotic medicine in children under 18 years of age. CIPRO Tablets, CIPRO Oral Suspension and CIPRO I.V. should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract

infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if CIPRO XR is safe and effective in children under 18 years of age.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including CIPRO, do not kill viruses.
Call your healthcare provider if you think your condition is not getting better while you are taking CIPRO.

Who should not take CIPRO?

Do not take CIPRO if you:

- have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in CIPRO. Ask your healthcare provider if you are not sure. See the list of ingredients in CIPRO at the end of this Medication Guide.
- also take a medicine called tizanidine (Zanaflex®). Serious side effects from tizanidine are likely to happen.

What should I tell my healthcare provider before taking CIPRO?

See "**What is the most important information I should know about CIPRO?**"
Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"
- have a history of seizures
- have kidney problems
- have rheumatoid arthritis (RA) or other history of joint problems
- have trouble swallowing pills
- are pregnant or planning to become pregnant. It is not known if CIPRO will harm your unborn child.
- are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. You and your healthcare provider should decide whether you will take CIPRO or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal and dietary supplements. CIPRO and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take CIPRO or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "What are the possible side effects of CIPRO?".
- a blood thinner (warfarin, Coumadin, Jantoven)

- tizanidine (Zanaflex®) You should not take CIPRO if you are already taking tizanidine. See "Who should not take CIPRO?"
- theophylline (Theo-24, Elixophyllin, Theochron, Uniphyl, Theolair)
- glyburide (Micronase, Glynase, Diabeta, Glucovance). See "What are the possible side effects of CIPRO?"
- phenytoin(Fosphenytoin Sodium, Cerebyx, Dilantin-125, Dilantin, Extended Phenytoin Sodium, Prompt Penytoin Sodium, Phenytek)
- products that contain caffeine
- a medicine to control your heart rate or rhythm (antiarrhythmics) See "What are the possible side effects of CIPRO?"
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about CIPRO**?"
- methotrexate (Trexall)
- Probenecid (Probalan, Col-probenecid)
- Metoclopromide (Reglan, Reglan ODT)
- Certain medicines may keep CIPRO Tablets, CIPRO Oral Suspension from working correctly. Take CIPRO Tablets and Oral Suspension either 2 hours before or 6 hours after taking these products:
- many antacids, multivitamins, and other dietary supplements that contain magnesium, calcium, aluminum, iron or zinc
- sulcrafate (Carafate)
- didanosine (Videx®, Videx EC®)

Ask your healthcare provider if you are not sure if any of your medicines are the kind listed above.
Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should CIPRO be taken?

- Take CIPRO exactly as prescribed by your healthcare provider.
- Take CIPRO Tablets in the morning and evening at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- Take CIPRO Oral Suspension in the morning and evening at about the same time each day. Shake the CIPRO Oral Suspension bottle well each time before use for about 15 seconds to make sure the suspension is mixed well. Close the bottle completely after use.

- Take CIPRO XR one time each day at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- CIPRO I.V. is given to you by intravenous (I.V.) infusion into your vein, slowly, over 60 minutes, as prescribed by your healthcare provider.
- CIPRO can be taken with or without food.
- CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking CIPRO.
- Do not skip any doses, or stop taking CIPRO even if you begin to feel better, until you finish the prescribed treatment, unless you have:
- tendon effects (see "What is the most important information I should know about CIPRO?"),
- a serious allergic reaction (see "What are the possible side effects of CIPRO?"), or
- your healthcare provider tells you to stop.

This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to CIPRO. If this happens, CIPRO and other antibiotic medicines may not work in the future.

- If you miss a dose of CIPRO Tablets or Oral Suspension, take it as soon as you remember. Do not take two doses at the same time, and do not take more than two doses in one day.
- If you miss a dose of CIPRO XR, take it as soon as you remember. Do not take more than one dose in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

If you have been prescribed CIPRO Tablets, CIPRO Oral Suspension or CIPRO I.V. for possible anthrax exposure:

- CIPRO Tablets, Oral Suspension and I.V. has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.
- In most cases, CIPRO Tablets, Oral Suspension and I.V. should not be used in children. CIPRO Tablets, Oral Suspension and I.V. are only approved for use in children younger than 18 years old for anthrax exposure and complicated urinary tract infections.
- Take your CIPRO exactly as prescribed by your healthcare provider. Do not stop taking your CIPRO without talking with your healthcare provider. If you stop taking your CIPRO too soon, it may not prevent you from getting the anthrax disease.
- Side effects may happen while you are taking CIPRO Tablets, Oral Suspension or I.V.. When taking your CIPRO to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping the medicine too soon are more important than the risks of side effects with CIPRO.

- If you are pregnant, or plan to become pregnant while taking CIPRO, you and your healthcare provider should talk about whether the benefits of taking CIPRO Tablets, Oral Suspension or I.V. for anthrax are more important than the risks.

What should I avoid while taking CIPRO?

CIPRO can make you dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how CIPRO affects you.

Avoid sunlamps, tanning beds, and try to limit your time in the sun. CIPRO can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking CIPRO, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of CIPRO?

CIPRO can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about CIPRO?**"

Other serious side effects of CIPRO include:

- **Central Nervous System Effects**

  Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking CIPRO will change your risk of having a seizure. Seizures have been reported in people taking fluoroquinolone antibiotics including CIPRO.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of CIPRO. Talk to your healthcare provider right away if you have any of these side effects, or other changes in mood or behavior:
  - feel dizzy
  - seizures
  - hearing voices, seeing things, or sensing things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - depression
  - trouble sleeping
  - nightmares
  - feel more suspicious (paranoia)
  - suicidal thoughts or acts

- **Serious allergic reactions**

Allergic reactions can happen in people taking fluoroquinolones, including CIPRO, even after only one dose. Stop taking CIPRO and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- faint
- **Yellowing of the skin or eyes.** Stop taking CIPRO and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to CIPRO (a liver problem).
- **Skin rash.** Skin rash may happen in people taking CIPRO. Stop taking CIPRO at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to CIPRO.
- **Serious heart rhythm changes** (QT prolongation and torsade de pointes)

Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. CIPRO may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:

- who are elderly
- with a family history of prolonged QT interval,
- with low blood potassium (hypokalemia),
- who take certain medicines to control heart rhythm (antiarrhythmics).
- **Intestine infection** (Pseudomembranous colitis)

Pseudomembranous colitis can happen with most antibiotics, including CIPRO. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**

Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including CIPRO. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your/their arms, hands, legs, or feet:

- pain
- burning
- tingling
- numbness
- weakness

  CIPRO may need to be stopped to prevent permanent nerve damage.

- **Low blood sugar** (hypoglycemia)

People taking CIPRO and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar

(hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with CIPRO. Your/their antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity)**

See "**What should I avoid while taking CIPRO?**"

- **Joint Problems**
- Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with CIPRO.

The most common side effects of CIPRO include:

- nausea
- headache
- diarrhea
- vomiting
- vaginal yeast infection
- changes in liver function tests
- pain or discomfort in the abdomen

These are not all the possible side effects of CIPRO. Tell your healthcare provider about any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CIPRO?

CIPRO Tablets

Store CIPRO below 86°F (30°C).

CIPRO Oral Suspension

- Store CIPRO Oral Suspension below 86°F (30°C) for up to 14 days.
- Do not freeze.
- After treatment has been completed, any unused oral suspension should be safely thrown away.

CIPRO XR

- Store CIPRO XR at 59°F to 86°F (15°C to 30°C).

Keep CIPRO and all medicines out of the reach of children.

General Information about CIPRO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CIPRO for a condition for which it is not prescribed. Do not give CIPRO to other people, even if they have the same symptoms that you have. It may harm them.
This Medication Guide summarizes the most important information about CIPRO. If you would like more information about CIPRO, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIPRO that is written for healthcare professionals. For more information go to www.CIPRO.com or call 1-800-526-4099.

What are the ingredients in CIPRO?

CIPRO Tablets:

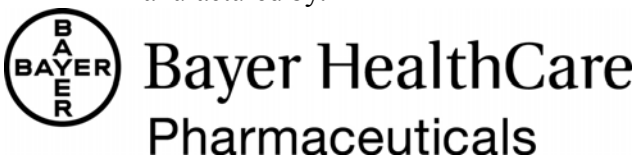
- Active ingredient: ciprofloxacin
- Inactive ingredients: cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol.

CIPRO Oral Suspension:

- Active ingredient: ciproflxacin
- Inactive ingredients: 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.
- CIPRO XR:
- Active ingredient: ciprofloxacin
- Inactive ingredients: crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.
- CIPRO I.V.:
- Active ingredient: ciprofloxacin
- Inactive ingredients: lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

Revised September 2008

Manufactured by:



Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Distributed by:

Schering Corporation
Kenilworth, NJ 07033

Rx Only

XXXXXXX, R.X 09/08

 Printed in U.S.A.

CIPRO (ciprofloxacin) 5% and 10% Oral Suspension Made in Italy
CIPRO (ciprofloxacin HCl) Tablets Made in Germany

This Medication Guide has been approved by the U.S. Food and Drug Administration.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kristen Miller
9/17/2008 03:37:28 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-068
NDA 19-847/S-042
NDA 19-857/S-049
NDA 20-780/S-026
NDA 21-473/S-024

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Dr. Herrington:

Please refer to your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Drug Product Name	**NDA Number**	**Supplement number**	**Date of supplement**	**Date of receipt**
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-068	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-042	August 5, 2008	August 6, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-049	August 5, 2008	August 6, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-026	August 5, 2008	August 6, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-024	August 5, 2008	August 6, 2008

On July 7, 2008, we sent a letter invoking our authority under section 505(o)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) to require safety related labeling changes to the labeling of CIPRO to address the risk of tendon-related adverse events with the use of fluoroquinolones based on new safety information about this risk identified since the drug was approved. You were directed to submit prior-approval supplements proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On August 5, 2008, you submitted prior-approval supplements that contained safety related labeling changes including a Medication Guide. Under section 505(o)(4)(C), FDA was to promptly review the supplement and if we disagreed with the proposed changes, initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30 day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling.

If you have any questions, please call Kristen Miller, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

9/5/2008 05:55:46 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2008

To: Janet Herrington, Ph.D.	**From:** Kristen Miller, Pharm.D.
Company: Bayer Pharmaceuticals Corp.	Division of Special Pathogen and Transplant Products
Email Address: janet.herrington.b@bayer.com	**Fax Number:** 301-796-9882
Phone Number:	**Phone Number:** 301-796-0762

Subject: Updated wording for SLR submissions

Total no. of pages including cover:

Comments: Concur:
Ozlem Belen, M.D. Deputy Director of Safety

Document to be mailed: ❑ YES ☑ NO

Please refer to your supplemental new drug applications (NDA) for CIPRO® (ciprofloxacin), NDAs 19-537/S-068, 19-847/S-042, 19-857/S-049, 20-780/S-026, and 21-473/S-024. Please also refer to our July 7, 2008 supplement request that changes be made to the labeling with regard to tendinitis and tendon rupture.

In response to our July 7, 2008 supplement request, we received counterproposals from all sponsors of fluoroquinolone products. We have reviewed all counterproposals and have made a few modifications to the wording from our original request based on the proposals. The changes to the labeling that the Agency is preparing to approve is below (additions are noted by underline and deletions are noted by ~~strikethrough~~). Please let me know if there are any errors.

Please note that the information regarding tendon effects was moved to the beginning of each respective subsection. The changes below are based on the current approved labeling.

We have also included the Medication Guide with our modifications based on sponsors' counterproposals. There were some proposals that were reasonable, but based on standard formatting for Medication Guides, we could not accept. The attached Medication Guide is our current proposal, but is currently undergoing review through other FDA Offices, so additional changes may be made (and the formatting will be finalized before approval).

Prior to approval of the supplements, we will need to receive formal concurrence from you on the content of the labeling.

We are providing this information via email for your convenience. Please contact me at 301-796-1600 if you have any questions.

_____

Kristen Miller, Pharm.D.
Safety Regulatory Project Manager

1. A **Boxed Warning** with bolded font and enclosed in a black box was added to the beginning of the labeling as follows:

> **WARNING:**
> **Fluoroquinolones, including CIPRO®, are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).**

2. The **WARNINGS/Tendon Effects** subsection of the labeling was renamed "**Tendinopathy and Tendon Rupture**", moved to the first paragraph of the **WARNINGS** section, and updated as follows:

   Tendinopathy and Tendon Rupture: Fluoroquinolones, including CIPRO, are associated with an increased risk of tendinitis and tendon rupture. This adverse reaction

most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIPRO should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

~~**Tendon Effects:** Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Ciprofloxacin 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 tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.~~

3. The information on tendon adverse reactions in the **PRECAUTIONS/ Information for Patients** subsection of the labeling was moved to the first bullet of the subsection and updated as follows:

- contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue CIPRO® treatment. The risk of severe tendon disorder with fluoroquinolones is increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- ~~to discontinue CIPRO treatment, rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those on corticosteroids.~~

4. The information on tendon adverse events in the **PRECAUTIONS/Geriatric Use** subsection of the labeling was moved to the first paragraph of the subsection and updated as follows:

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as AVELOX. This risk is

further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing AVELOX to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue AVELOX and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

~~Patients over 65 years of age are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendon rupture usually involves the Achilles, hand or shoulder tendons and can occur during therapy or up to a few months post completion of therapy. Caution should be used when prescribing CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue therapy and inform their physicians if any tendon symptoms occur.~~

5. The Patient Package Insert was replaced with a Medication Guide as follows:

MEDICATION GUIDE

CIPRO® *(Sip-row)*
(ciprofloxacin hydrochloride)
TABLETS

CIPRO® *(Sip-row)*
(ciprofloxacin)
ORAL SUSPENSION

CIPRO® XR *(Sip-row)*
(ciprofloxacin extended-release tablets)

CIPRO® I.V. *(Sip-row)*
(ciprofloxacin)
For Intravenous Infusion

Read the Medication Guide that comes with CIPRO® completely before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CIPRO?
CIPRO is a fluoroquinolone antibiotic medicine. CIPRO can cause side effects that may be serious or even cause death. If you develop any of the following serious side effects, get medical help right away, and talk with your healthcare provider about whether you should continue taking CIPRO.

- **Tendon rupture** Note: Tendons are the tough cords of tissue that connect muscles to bones.
- Pain, swelling, tears and inflammation of tendons including the Achilles, shoulder, hand, or other tendon sites can happen in patients taking fluoroquinolone antibiotics, including CIPRO. The risk of getting tendon problems is higher if you:
    - are over 60 years of age
    - are taking steroids (corticosteroids)
    - have had a kidney, heart, or lung transplant
    - Other reasons for tendon ruptures can include:
        - physical activity or exercise
        - kidney failure
        - tendon problems in the past, such as in patients with rheumatoid arthritis (RA)
    - Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking CIPRO until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle; however, this can occur with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of CIPRO and whether you need to be prescribed a different non-fluoroquinolone antibiotic to treat your infection.
    - Get medical help right away if you have any of the following signs or symptoms of a tendon rupture:
        - hear or feel a snap or pop in a tendon area
        - bruising right after an incident in a tendon area
        - unable to move the affected area or bear weight

What is CIPRO?

CIPRO is an antibiotic medicine (called a fluoroquinolone) used to treat infections caused by certain types of bacteria (germs). CIPRO Tablets, Oral Suspension, and I.V. are used to treat prostate, cervix, abdominal, lung, sinus, bone, urinary tract and skin infections. CIPRO Tablets, Oral Suspension, and I.V. kills many of the types of bacteria that cause infections in these sites. CIPRO XR is used to treat urinary tract and kidney infections. CIPRO XR should not be used to treat other infections.

CIPRO does not work for the treatment of syphilis.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including CIPRO, do not kill viruses.
Call your healthcare provider if you think your condition is not getting better while you are taking CIPRO.

Who should not take CIPRO?

- Do not take CIPRO if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone. Ask your healthcare provider if you are not sure.

- You should not take CIPRO if you are also taking a medication called tizanidine (Zanaflex®), as excessive side effects from tizanidine are likely to occur.
- Due to possible side effects, CIPRO is not recommended for persons less than 18 years of age except for specific serious infections, such as complicated urinary tract infections and the prevention of anthrax after inhalational exposure. Children have a higher chance of getting bone and joint problems (musculoskeletal) while taking CIPRO.

What should I tell my healthcare provider before taking CIPRO?
See "**What is the most important information I should know about CIPRO?**"
Tell your healthcare provider about all your medical conditions, including if you:

have tendon problems

have central nervous system problems

have nerve problems

or anyone in your family has an irregular heartbeat, especially a condition called "QTc prolongation"

have a history of seizures

have kidney problems

have rheumatoid arthritis (RA)

are pregnant or planning to become pregnant. It is not known if CIPRO will harm your unborn child.

are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. The effects of CIPRO on the nursing infant are unknown.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal and dietary supplements. CIPRO and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take CIPRO or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of CIPRO?**".

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

a medicine to thin your blood (called oral anticoagulants) such as warfarin (Coumadin, Jantoven)

tizanidine (Zanaflex®)

theophylline

glyburide

phenytoin

a medicine to control your heart rate or rhythm called "antiarrhythmics" See "**What are the possible side effects of CIPRO?**"

an anti-psychotic medicine

a tricyclic antidepressant

a water pill (diuretic)

a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about CIPRO?**"

Ask your healthcare provider if you are not sure if any of your medicines are the kind listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take CIPRO?

CIPRO Tablets

Unless directed otherwise by your healthcare provider, CIPRO should be taken twice a day.

Take CIPRO in the morning and evening at about the same time.

CIPRO can be taken with or without food.

CIPRO should not be taken with just dairy products or calcium-fortified juices alone, but may be taken with a meal that contains these products.

Do not skip any doses, or stop taking CIPRO even if you begin to feel better, until you finish your prescribed treatment, unless you experience tendon effects (see "**What is the most important information I should know about CIPRO?**"), a serious allergic reaction (see "**What are the possible side effects of CIPRO?**"), or your healthcare provider tells you to stop. This will help make sure that all of the bacteria are killed and decrease the chance that the bacteria will become resistant to CIPRO. If this happens, CIPRO and other antibiotic medicines may not work in the future.

If you miss a dose of CIPRO by mistake, do not take two doses at the same time.

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.

CIPRO XR

- CIPRO XR should be taken once a day for (3) to fourteen (14) days.
- Take CIPRO XR at approximately the same time each day.
- CIPRO XR can be taken with or without food.
- CIPRO XR should not be taken with just dairy products or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- **Swallow the CIPRO XR tablet whole. DO NOT SPLIT, CRUSH OR CHEW THE TABLET.**

- If you miss a dose of CIPRO XR, take it as soon as you remember. You should not take two doses in the same day.

CIPRO I.V.

- CIPRO I.V. should be administered by INTRAVENOUS infusion only.
- CIPRO I.V. should be administered by intravenous infusion over a period of 60 minutes, as prescribed by your healthcare provider.
- CIPRO I.V. should be administered to children at dosages prescribed by the physician.

If you have been prescribed CIPRO Tablets, Oral Suspension or I.V. for possible anthrax exposure:

- CIPRO Tablets, Oral Suspension or I.V. has been approved to lessen the chance of developing anthrax infection after you are exposed to the anthrax bacteria.
- In most cases, CIPRO Tablets, Oral Suspension or I.V. should not be used in children. CIPRO Tablets, Oral Suspension or I.V. is approved for use in people younger than 18 years old for anthrax exposure.
- Take CIPRO Tablets, Oral Suspension or I.V. exactly as prescribed by your healthcare provider. Do not stop taking CIPRO Tablets, Oral Suspension or I.V. without talking with your healthcare provider. If you stop taking CIPRO Tablets, Oral Suspension or I.V. too soon, it may not prevent you from getting the anthrax disease.
- Side effects may happen while you are taking CIPRO Tablets, Oral Suspension or I.V.. When taking CIPRO Tablets, Oral Suspension or I.V. to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping your medicine too soon are more important than the risks of side effects with CIPRO Tablets, Oral Suspension or I.V..

If you are pregnant, or plan to become pregnant while taking CIPRO Tablets, Oral Suspension or I.V., you and your healthcare provider should discuss if the benefits of taking CIPRO Tablets, Oral Suspension or I.V. for anthrax outweigh the risks.

What should I avoid while taking CIPRO?

CIPRO can cause dizziness. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how CIPRO affects you.

Avoid excessive exposure to sunlight, sunlamps and tanning beds. CIPRO can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking CIPRO, call your healthcare provider right away. Use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

CIPRO has been associated with an increased rate of side effects with joints and surrounding structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint related problems that occur during or following CIPRO therapy.

What are the possible side effects of CIPRO?
CIPRO can cause side effects that may be serious or even cause death. Serious side effects that can occur with use of CIPRO are also discussed in "**What is the most important information I should know about CIPRO?**"

Other serious side effects of CIPRO include:

- **Central Nervous System Effects**

Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking CIPRO will change your risk of having a seizure. Seizures have been reported in patients taking fluoroquinolone antibiotics including CIPRO.

Central Nervous System (CNS) side effects may occur as soon as after taking the first dose of CIPRO. Talk to your healthcare provider right away if you experience any of these side effects, or other changes in mood or behavior:

- seizures
- hallucinations (also known as imagining something that is not there)
- restlessness
- tremors
- anxiety
- confusion
- depression
- insomnia
- nightmares
- lightheadedness
- paranoia (also known as a feeling of being harassed or persecuted)
- suicidal thought or acts

- **Anaphylactic and serious allergic reactions**

Allergic reactions can happen in people taking fluoroquinolones, including CIPRO, even after only one dose. Stop taking CIPRO and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- **Skin rash.** Skin rash may occur in patients taking CIPRO. Stop taking CIPRO at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to CIPRO.
- Serious heart rhythm changes (QTc prolongation and torsade de pointes)

Tell your healthcare provider right away if you have a change in the way your heart beats (get a fast or irregular heartbeat), or if you faint. CIPRO may cause a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are increased in those:

- with a family history of prolonged QT interval,
- with low potassium (hypokalemia),
- and those who are taking drugs to control heart rhythm, called class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.
- Intestine infection (Pseudomembranous colitis)

Pseudomembranous colitis can happen with most antibiotics, including CIPRO. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen up to 2 months after you have finished your antibiotic.

- Changes in sensation and possible nerve damage (Peripheral Neuropathy)

Damage to the nerves in arms, hands, legs, or feet can happen in patients receiving fluoroquinolones, including CIPRO. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- pain
- burning
- tingling
- numbness
- weakness

CIPRO may need to be stopped to prevent permanent nerve damage.

- **Changes in blood sugar**

People taking CIPRO and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. Tell your healthcare provider if you get low blood sugar with CIPRO. Your antibiotic medicine may need to be changed.

- Sensitivity to sunlight (photosensitivity)

See **"What should I avoid while taking CIPRO?"**

The most common side effects of CIPRO include nausea, headache, diarrhea, vomiting, abdominal pain/discomfort, vaginal yeast infection, abnormal liver function tests, rash and dizziness.

These are not all the possible side effects of CIPRO. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CIPRO?

CIPRO Tablets

CIPRO should be stored below 30°C (86°F).

CIPRO Oral Suspension

- Ciprofloxacin microcapsules and diluent should be stored below 25°C (77°F). Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing.

CIPRO XR

- CIPRO XR should be stored at room temperature 25°C (77°F). A range of 15–30°C (59–86°F) is permitted.

CIPRO I.V.

- CIPRO I.V. vials should be stored between 5–30°C (41–86°F).
- CIPRO I.V. flexible containers should be stored between 5–25°C (41–77°F).
- Protect from light, avoid excessive heat, protect from freezing.

Keep CIPRO and all medicines out of the reach of children.

General Information about CIPRO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CIPRO for a condition for which it is not prescribed. Do not share CIPRO with other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about CIPRO. If you would like more information about CIPRO, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIPRO that is written for healthcare professionals. For more information go to www.CIPRO.com or call 1-800-526-4099.

What are the ingredients in CIPRO?

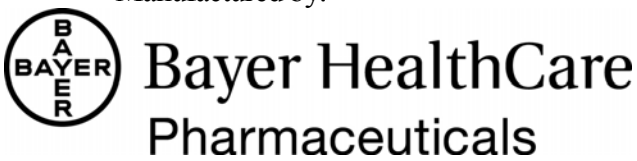
CIPRO Tablets contain:

- Active ingredient: ciprofloxacin
- Inactive ingredients: cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol.
- CIPRO Oral Suspension contains:
- Active ingredient: ciproflxacin
- Inactive ingredients: 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.
- CIPRO XR contains:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.
- CIPRO I.V. contains:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

August 2008

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:



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Wayne, NJ 07470

Distributed by:

Schering Corporation
Kenilworth, NJ 07033

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Rx Only

XXXXXXX, R.X 08/08

 Printed in U.S.A.

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

CIPRO (ciprofloxacin HCl) Tablets Made in Germany

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