CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-537 / S-041
20-780 / S-011

Trade Name: Cipro

Generic Name: Ciprofloxacin

Sponsor: Bayer Corporation

Approval Date: April 17, 2002
APPLICATION NUMBER:

19-537/S-041
20-780/S-011

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APPLICATION NUMBER:

19-537/S-041
20-780/S-011

APPROVAL LETTER
2. CLINICAL PHARMACOLOGY
• New subheadings (Absorption, Distribution, Metabolism, Excretion and Special Populations) were added to this section and existing information was reorganized under the new subheadings.

• Under Absorption, the following sentence was added and is now the third sentence in the second paragraph:

  The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

• The Microbiology subsection was completely revised.

3. The order of the indications in the INDICATIONS AND USAGE section was revised.

4. PRECAUTIONS
• The first bullet under Information for Patients was revised to read:

  • 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, or with other products containing calcium, iron or zinc should be avoided. These products Ciprofloxacin may be taken two hours after or six hours before ciprofloxacin, before or six hours after taking these products. Ciprofloxacin should not be taken concurrently with milk or yogurt alone dairy products (like milk or with yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption; however, ciprofloxacin may be taken with a meal that contains these products.

• The following paragraph was deleted in the Drug Interactions subsection:

  As with other broad-spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient’s condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

• The Pregnancy: Teratogenic Effects. Pregnancy Category C subsection was revised to read:

  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.\footnote{7}

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.\footnote{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).\footnote{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.\footnote{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, 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. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

- The following sentence was added to the Nursing Mothers subsection:

"The amount of ciprofloxacin absorbed by the nursing infant is unknown."
5. ADVERSE REACTIONS

The first paragraph in this section was revised to read:

During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%. 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 3.5% of patients treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The following adverse events were added to this subsection:

BODY AS A WHOLE: foot pain

HEMICO/LYMPHATIC: lymphadenopathy

The following sentence was deleted after the list of additional events:

"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."

The following paragraph was deleted (was the fourth paragraph in this section):

In domestic clinical trials involving 214 patients receiving a single 250 mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3% 1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.

In the Post-Marketing Adverse Events subsection, the following paragraph was added to replace the table of adverse events that previously existed:

agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspnea, dysphagia, erythema multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia, hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia gravis (possible exacerbation), myoclonus, nyctagmus, pancreatitis, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste loss, tendinitis, tendon
rupture, toxic epidermal necrolysis, triglyceride elevation (serum), vaginal candidiasis, and vasculitis (See PRECAUTIONS.)

6. OVERDOSAGE
- The following sentence was moved and is now the last sentence in this section:

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.

7. The DOSAGE AND ADMINISTRATION section was completely revised.

8. HOW SUPPLIED
- The paragraph and table concerning Cipro Oral Suspension were revised as follows:

CIPRO® Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist, are mixed prior to dispensing. See Instructions To The Pharmacist For Use/Handling.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Total volume after reconstitution</th>
<th>Ciprofloxacin Concentration contents after reconstitution</th>
<th>Ciprofloxacin contents per bottle</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>100 mL</td>
<td>250 mg/5 mL</td>
<td>5,000 mg</td>
<td>0026-8551-36</td>
</tr>
<tr>
<td>10%</td>
<td>100 mL</td>
<td>500 mg/5 mL</td>
<td>10,000 mg</td>
<td>0026-8553-36</td>
</tr>
</tbody>
</table>

9. The previous CLINICAL STUDIES section was deleted and replaced by the following:

Uncomplicated Cystitis

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

10. Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension

- The following information was added to the beginning of this section:
CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g 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:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>250-mg</td>
<td>5 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>500-mg</td>
<td>10 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>750-mg</td>
<td>15 mL</td>
<td>7.5 mL</td>
</tr>
</tbody>
</table>

- The following sentences were added to this section:

**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.**

11. **Instructions To The Patient For Taking CIPRO® Oral Suspension** was deleted since a new patient package insert has been added to the end of this label.

12. Three new references were added to the **REFERENCES** section.

13. A new section called "**PATIENT INFORMATION ABOUT CIPRO® (ciprofloxacin hydrochloride) TABLETS, CIPRO® (ciprofloxacin) ORAL SUSPENSION**" was added.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions noted below. Accordingly, the supplemental applications are approved effective on the date of this letter.

1. In the **CLINICAL PHARMACOLOGY** section, **Microbiology** subsection, "*Acinetobacter Iwoffii*" is spelled incorrectly. Replace 'Iwoffii' with "Iwoffii".

2. Please correct the spelling of the word "discarded" in the following sentence located in the "**Patient Information About Cipro**" section, **Cipro Oral Suspension** subsection of the package insert:

"After treatment has been completed, any remaining suspension should be discarded."
The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (package insert submitted April 1, 2002). These revisions are a term of the approval of these applications.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-537/S-041, NDA 20-780/S-011." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
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/

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Renata Albrecht
4/17/02 05:10:31 PM
NDA 19-537/S-041
NDA 20-780/S-011

Bayer Corporation Pharmaceutical Division
Attention: Robin Christoforides
Assistant Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

APPEARS THIS WAY ON ORIGINAL

Dear Ms. Christoforides:

Please refer to your supplemental new drug applications dated December 22, 2000, received December 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg, 750 mg, and Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%.

We acknowledge receipt of your submission dated June 22, 2001.

These supplements propose the following change(s):
1. Multiple changes to the package insert to be more consistent with current labeling standards.
2. Length of the package insert shortened to make the package insert more physician friendly (Clinical Studies section deleted)
3. Microbiology changes incorporated as proposed by the Agency
4. New Patient Information section (PPI) added

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved however, it will be necessary for you to submit draft labeling revised as follows [Note these revisions were previously communicated in our faxes dated December 19, 2001 and January 14, 2002]:

1. PRECAUTIONS, Information for Patients

Please delete the following sentence that appears at the end of the first bullet since this is an unresolved issue and does not provide clear guidance:


2. PRECAUTIONS

Please replace the current wording with the following:

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. Controlled prospective observational d

**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.

3. **CLINICAL STUDIES**

Please replace the **CLINICAL STUDIES** section as it appears in the last approved label.

4. **Patient Information**

Please replace the proposed wording with the following:

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

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. CIPRO can be prescribed only by a licensed physician.

Only your doctor can determine if CIPRO is right for you.

What is CIPRO?

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:
Unless directed otherwise by your physician, CIPRO should be taken twice a day, at approximately the same time, in the morning and in the evening.

CIPRO 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.

Who should not take CIPRO?
You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as “quinolones”.

CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant, or plan to become pregnant while taking CIPRO,
Side effects caused by CIPRO may be acceptable for treating or preventing serious infections such as anthrax. However, when a person does not have a serious infection, or has not been exposed to anthrax, the treatment benefit may not equal the risk of side effects. You and your doctor should discuss the risks of taking any medicine against the good it may do.

What are the possible side effects of Cipro?

Cipro is generally well tolerated. The most common side effects caused by CIPRO, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort.

Remember:

Do not give CIPRO to anyone other than the person for which it was prescribed.
Take your dose of CIPRO in the morning and in the evening.

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

Keep CIPRO and all medications out of reach of children.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw these supplemental applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
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/
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Renata Albrecht
1/31/02 03:25:07 PM

Appears this way on original
APPLICATION NUMBER:

19-537/S-041
20-780/S-011

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

PZXXXXXX

DESCRIPTION

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, 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 C₁₇H₁₇FN₃O₃•HCl•H₂O and its chemical structure is as follows:

![Chemical Structure of Ciprofloxacin]

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is C₁₇H₁₇FN₃O₃ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:

![Chemical Structure of Ciprofloxacin]

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

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

Microcapsules - ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropyl methylcellulose, magnesium stearate, and Polysorbate 20.
Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

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

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Maximum Serum Concentration (µg/mL)</th>
<th>Area Under Curve (AUC) (µg·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>500</td>
<td>2.4</td>
<td>11.6</td>
</tr>
<tr>
<td>750</td>
<td>4.3</td>
<td>20.2</td>
</tr>
<tr>
<td>1000</td>
<td>5.4</td>
<td>30.8</td>
</tr>
</tbody>
</table>

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 mg/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.

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>500 mg</th>
<th>400 mg</th>
<th>750 mg</th>
<th>400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>q_{12h}, P.O.</td>
<td>13.7^a</td>
<td>12.7^a</td>
<td>31.6^b</td>
<td>32.9^c</td>
</tr>
<tr>
<td>q_{12h}, I.V.</td>
<td>2.97</td>
<td>4.56</td>
<td>3.59</td>
<td>4.07</td>
</tr>
<tr>
<td>AUC (µg·hr/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aAUC 0-12h = AUC_{0-12h}^x2  ^bAUC_{24h} = AUC_{0-12h}^x2  ^cAUC_{24h} = AUC_{0-8h}^x2

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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.

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 of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient development CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See PRECAUTIONS.)

Special Populations: Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. Although the Cmax 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.

**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 parainfluenza 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 lwoffii    Pasteurella multocida
Aeromonas hydrophilia   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 (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:
For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

For testing *Neisseria gonorrhoeae*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.06</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.12 – 0.5</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 1</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>ATCC 29212</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>ATCC 49226</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 29213</td>
</tr>
</tbody>
</table>

*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 procedure2 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-20</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*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% CO₂.

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

<table>
<thead>
<tr>
<th>Zone Diameter(mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

*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*:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 41</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>28 – 40</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤ 27</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td></td>
<td>30-40</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td></td>
<td>34-42</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>ATCC 49226</td>
</tr>
<tr>
<td></td>
<td>48-58</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td></td>
<td>25-33</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 25923</td>
</tr>
<tr>
<td></td>
<td>22-30</td>
</tr>
</tbody>
</table>

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

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

**INDICATIONS AND USAGE**

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

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

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


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

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

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

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

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

**Infectious Diarrhea** caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii*, *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*.

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

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. (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.

**CONTRAINDICATIONS**

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

**WARNINGS**

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE) - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

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

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.
Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

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

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

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

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

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

**PRECAUTIONS**

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

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

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

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.
As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

**Information for Patients:**

- 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, or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these products.

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

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

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

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

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

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

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

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

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

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

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

The concomitant administration of ciprofloxacin with the 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 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.

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

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

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

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

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

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the
time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1)
mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks
while concurrently being administered ciprofloxacin. The time to development of the first skin
tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose
approximately equal to maximum recommended human dose based upon mg/m²), as opposed
to 34 weeks when animals were treated with both UVA and vehicle. The times to development
of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other
quinolones.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 (0.8 times the
highest recommended human dose of 1200 mg based upon body surface area) revealed no
evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. An expert review of
published data on experiences with ciprofloxacin use during pregnancy by THERIS – 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,
ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See WARNINGS.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established, except for use in inhalational anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

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

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin 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.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group.

Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

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

ADVERSE REACTIONS
During clinical investigation with the tablet, 2,799 patients received 2,868 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 3.5% of patients treated.
The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%),
vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and
rash (1.1%).
Additional events that occurred in less than 1% of ciprofloxacin patients are listed below.

BODY AS A WHOLE: foot pain
CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension,
angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis
CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia,
nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive
seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia,
depersonalization, depression, paresthesia (See above.) (See
PRECAUTIONS.)
GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia,
intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic
jaundice has been reported.
HEMIC/LYMPHATIC: lymphadenopathy
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: pruritus, urticaria, photosensitivity, flushing, fever,
chills, angioedema, edema of the face, neck, lips, conjunctivae or hands,
cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)
Allergic reactions ranging from urticaria to anaphylactic reactions have been
reported. (See WARNINGS.)
SPECIAL SENSES: blurred vision, disturbed vision (change in color
perception, overbrightness of lights), decreased visual acuity, diplopia, eye
pain, tinnitus, hearing loss, 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 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.

**Post-Marketing Adverse Events:** Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:

- agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia, hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), vaginal candidiasis, and vasculitis (See **PRECAUTIONS**).

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

**Hepatic** - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

**Hematologic** - Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

**Renal** - Elevations of serum creatinine (1.1%), BUN (0.9%), CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: elevation of serum 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, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. 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**

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

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

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable / buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.
<table>
<thead>
<tr>
<th>Infection</th>
<th>Type or Severity</th>
<th>Unit Dose</th>
<th>Frequency</th>
<th>Usual Durations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract</td>
<td>Acute Uncomplicated</td>
<td>100 mg or 250 mg</td>
<td>q 12 h</td>
<td>3 Days</td>
</tr>
<tr>
<td></td>
<td>Mild/Moderate</td>
<td>250 mg</td>
<td>q 12 h</td>
<td>7 to 14 Days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>7 to 14 Days</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>26 Days</td>
</tr>
<tr>
<td>Lower Respiratory Tract</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>7 to 14 days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>750 mg</td>
<td>q 12 h</td>
<td>7 to 14 days</td>
</tr>
<tr>
<td>Acute Sinusitis</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>10 days</td>
</tr>
<tr>
<td>Skin and Skin Structure</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>7 to 14 Days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>750 mg</td>
<td>q 12 h</td>
<td>7 to 14 Days</td>
</tr>
<tr>
<td>Bone and Joint</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>≥ 4 to 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>750 mg</td>
<td>q 12 h</td>
<td>≥ 4 to 6 weeks</td>
</tr>
<tr>
<td>Intra-Abdominal*</td>
<td>Complicated</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>7 to 14 Days</td>
</tr>
<tr>
<td>Infectious Diarrhea</td>
<td>Mild/Moderate/Severe</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>5 to 7 Days</td>
</tr>
<tr>
<td>Typhoid Fever</td>
<td>Mild/Moderate</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>10 Days</td>
</tr>
<tr>
<td>Urethral and Cervical Gonococcal Infections</td>
<td>Uncomplicated</td>
<td>250 mg</td>
<td>single dose</td>
<td>single dose</td>
</tr>
<tr>
<td>Inhalational anthrax (post-exposure)**</td>
<td>Adult</td>
<td>500 mg</td>
<td>q 12 h</td>
<td>60 Days</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>15 mg/kg per dose, not to exceed 500 mg</td>
<td>q 12 h</td>
<td>60 Days</td>
</tr>
</tbody>
</table>

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
** Drug administration should begin as soon as possible after suspected or confirmed exposure.
This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit. For a discussion of ciprofloxacin serum concentrations in various human populations, see INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.

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

Equivalent AUC Dosing Regimens

<table>
<thead>
<tr>
<th>Cipro Oral Dosage</th>
<th>Equivalent Cipro I.V Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg Tablet q 12 h</td>
<td>200 mg I.V. q 12 h</td>
</tr>
<tr>
<td>500 mg Tablet q 12 h</td>
<td>400 mg I.V. q 12 h</td>
</tr>
<tr>
<td>750 mg Tablet q 12 h</td>
<td>400 mg I.V. q 8 h</td>
</tr>
</tbody>
</table>

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

**RECOMMENDED STARTING AND MAINTENANCE DOSES**

**FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>See Usual Dosage.</td>
</tr>
<tr>
<td>30 - 50</td>
<td>250-500 mg q 12 h</td>
</tr>
<tr>
<td>5 - 29</td>
<td>250-500 mg q 18 h</td>
</tr>
<tr>
<td>Patients on hemodialysis or Peritoneal dialysis</td>
<td>250-500 mg q 24 h (after dialysis)</td>
</tr>
</tbody>
</table>

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

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

Women: $0.85 \times$ the value calculated for men.

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

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

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

**HOW SUPPLIED**

CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-
coated tablets containing 100 mg or 250 mg ciprofloxacin. The 100 mg tablet is coded with the
word “CIPRO” on one side and “100” on the reverse side. The 250 mg tablet is coded with the
word “CIPRO” on one side and “250” on the reverse side. CIPRO is also available as capsule
shaped, slightly yellowish film-coated tablets containing 500-mg or 750 mg ciprofloxacin. The
500 mg tablet is coded with the word “CIPRO” on one side and “500” on the reverse side. The
750 mg tablet is coded with the word “CIPRO” on one side and “750” on the reverse side.
CIPRO 250 mg, 500 mg, and 750 mg are available in bottles of 50, 100, and Unit Dose
packages of 100. The 100 mg strength is available only as CIPRO Cystitis pack containing 6
tables for use only in female patients with acute uncomplicated cystitis.
<table>
<thead>
<tr>
<th>Strength</th>
<th>NDC Code</th>
<th>Tablet Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottles of 50:</td>
<td>750 mg</td>
<td>NDC 0026-8514-50</td>
</tr>
<tr>
<td>Bottles of 100: 250 mg</td>
<td>NDC 0026-8512-51</td>
<td>CIPRO 250</td>
</tr>
<tr>
<td>500 mg</td>
<td>NDC 0026-8513-51</td>
<td>CIPRO 500</td>
</tr>
</tbody>
</table>

Unit Dose

| Package of 100:  | 250 mg            | NDC 0026-8512-48      | CIPRO 250             |
| 500 mg           | NDC 0026-8513-48  | CIPRO 500             |
| 750 mg           | NDC 0026-8514-48  | CIPRO 750             |

Cystitis

| Package of 6:    | 100 mg            | NDC 0026-8511-06      | CIPRO 100             |

Store below 30°C (86°F).

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

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Total volume after reconstitution</th>
<th>Ciprofloxacin Concentration</th>
<th>Ciprofloxacin contents per bottle</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>100 mL</td>
<td>250 mg/5 mL</td>
<td>5,000 mg</td>
<td>0026-8551-36</td>
</tr>
<tr>
<td>10%</td>
<td>100 mL</td>
<td>500 mg/5 mL</td>
<td>10,000 mg</td>
<td>0026-8553-36</td>
</tr>
</tbody>
</table>

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

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

ANIMAL PHARMACOLOGY

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

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 dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV 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 IV 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**

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

**INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See DOSE 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.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD₅₀ (~5.5 x 10⁵ spores range 5-30 LD₅₀) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 μg/ml. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected Tmax (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. 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

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

CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g 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:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>5 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>500 mg</td>
<td>10 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>750 mg</td>
<td>15 mL</td>
<td>7.5 mL</td>
</tr>
</tbody>
</table>

**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:
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).

PATIENT INFORMATION ABOUT

CIPRO® (ciprofloxacin hydrochloride) TABLETS

CIPRO® (ciprofloxacin) ORAL SUSPENSION

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

What is CIPRO?

CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria that can infect these areas of the body. CIPRO has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your condition is not improving while taking CIPRO.

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:

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

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

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

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones".

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

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

What are the possible side effects of CIPRO?

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

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

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

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

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

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.
What about other medications I am taking?

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

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

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

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

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

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

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

Remember:

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

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

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

Keep CIPRO and all medications out of reach of children.

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516 USA
Rx Only
CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition".
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
4/17/02 05:10:31 PM
APPLICATION NUMBER:

19-537/S-041
20-780/S-011

MEDICAL AND CHEMISTRY REVIEW
Labeling and Clinical Review of Supplemental Labeling Revisions (SLR):

Materials Reviewed:

<table>
<thead>
<tr>
<th>Product</th>
<th>NDA #</th>
<th>SLR #</th>
<th>Letter Date</th>
<th>Receipt Date</th>
<th>Completed Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRO® (ciprofloxacin) Tablets, 100 mg, 250 mg, 500 mg, 750 mg</td>
<td>19-537</td>
<td>041</td>
<td>December 22, 2000</td>
<td>December 26, 2000</td>
<td>January 30, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%, 250 mg, 500 mg</td>
<td>20-780</td>
<td>011</td>
<td>December 22, 2000</td>
<td>December 26, 2000</td>
<td>January 30, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg</td>
<td>19-847</td>
<td>026</td>
<td>January 11, 2001</td>
<td>January 12, 2001</td>
<td>January 30, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg</td>
<td>19-857</td>
<td>028</td>
<td>January 11, 2001</td>
<td>January 12, 2001</td>
<td>January 30, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg (never launched)</td>
<td>19-858</td>
<td>022</td>
<td>January 11, 2001</td>
<td>January 12, 2001</td>
<td>January 30, 2002</td>
</tr>
<tr>
<td>Amendment</td>
<td>19-858</td>
<td>022</td>
<td>June 29, 2001</td>
<td>July 2, 2001</td>
<td>January 30, 2002</td>
</tr>
</tbody>
</table>

• Approved package insert for NDAs 19-537 and 20-780 dated August 30, 2000
• Approved package insert for NDAs 19-847 and 19-857 dated August 30, 2000
• FDA fax to Bayer concerning proposed Microbiology labeling revisions dated June 29, 2000
• FDA fax to Bayer concerning miscellaneous proposed labeling revisions dated March 5, 2001
• FDA fax to Bayer concerning FDA’s s recommended pregnancy labeling revisions dated December 19, 2001
• FDA fax to Bayer concerning proposed Patient Information section (PPI) revisions dated January 14, 2002

Sponsor: Bayer Corporation Pharmaceutical Division

Background:
Cipro Tablet/Oral Suspension:
Ciprofloxacin (CIPRO®) is a fluoroquinolone antibacterial agent. NDA 19-537 (tablet) was originally approved on October 22, 1987. NDA 20-780 (oral suspension) was originally approved on September 26, 1997. The tablet and oral suspension have shared one label since that time. The most recent labeling approval for these NDAs occurred on August 30,2000. No other labeling changes have been approved since that date.
Cipro IV Formulation:
NDA 19-847 (IV/vial), NDA 19-857 (IV/Flexibag with Dextrose) and NDA 19-858 (IV/Flexibag with NaCl) were originally approved on December 26, 1990. The IV/vial and the IV/flexibag with Dextrose have shared a label since that time. The last approved labeling changes occurred on August 30, 2000. No other labeling changes have been approved since that time. The IV/Flexibag with NaCl was never launched by the company, and does not currently appear in the IV labeling.

These labeling supplements for prior approval submitted to all of the Cipro NDAs noted above in December 2000/January 2001 provide for multiple changes to the package inserts in order to be more consistent with current labeling standards. The length was shortened to "make the package insert more physician friendly while maintaining all pertinent and required information." Microbiology labeling changes proposed by Peter Dionne, Microbiology Reviewer and faxed to the company on June 29, 2000 were also included in these submissions. A new Patient Information section (PPI) was also added.

Following the initial review of these labeling supplements by Dr. Eileen Navarro, Medical Officer and Mr. Dionne's Microbiology review dated February 9, 2001, the following revisions were proposed for the Cipro labels. These were faxed to Bayer on March 5, 2001:

Clinical Reviewer Comments:
1. The clinical pharmacology section should be revised to include information in the following subsections: Absorption, Distribution, Metabolism, Excretion, Special Populations

2. The order of the approved indications should be maintained as in the original label.

3. The spelling of Administration in Line 926 should be corrected.

4. The equivalent oral and IV doses should be displayed in a table, following lines 985-7.

5. The section “Instructions to the Pharmacist” and “Instructions to the Patient” should be retained in its original location in the label.

6. The Clinical Studies section should be retained.

Microbiology Reviewer Comments:

7. In line 171 the words In vitro should be in italic in the sentence that begins "In vitro resistance to ciprofloxacin develops slowly …

8. Staphylococcus aureus and Staphylococcus epidermidis in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of.

9. Streptococcus pneumoniae in lines 195 and 249 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of.

Revised labels for the Cipro NDAs incorporating the proposed FDA revisions noted in the March 5, 2001 fax were submitted by Bayer on June 22, 2001, received June 25, 2001.
Electronic Labeling Comparisons:

Strikeout=deleted
Double underline=added

Cipro Tablet/Oral Suspension label
The approved package insert for NDA 19-537 (Tablet) and NDA 20-780 (Oral Suspension) dated August, 2000 was electronically compared to the proposed draft labeling dated June 22, 2001, received June 25, 2001. The changes were as follows:

1. DESCRIPTION
   • The description of tablet color and the addition of "corn" to the word "starch" were added as follows:

   Ciprofloxacin tablets are white to slightly yellowish, CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

2. CLINICAL PHARMACOLOGY
   • As we requested, new subheadings were added to this section and existing information was reorganized under the following; Absorption, Distribution, Metabolism, Excretion and Special Populations.

   • Under Absorption, the following sentence was added and is now the third sentence in the second paragraph:

     The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

   • The Microbiology subsection was revised as follows:

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-<sub>(ciprofloxacin hydrochloride) Tablets and CIPRO — (ciprofloxacin) 5% and 10% Oral Suspension.

**Aerobic gram-positive microorganisms**

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

**Aerobic gram-negative microorganisms**

- *Campylobacter jejuni*  
- *Citrobacter diversus*  
- *Citrobacter freundii*  
- *Enterobacter cloacae*  
- *Escherichia coli*  
- *Haemophilus influenzae*  
- *Haemophilus parainfluenzae*  
- *Klebsiella pneumoniae*  
- *Moraxella catarrhalis*  
- *Morganella morganii*  
- *Neisseria gonorrhoeae*  

Delete I.V. microorganisms as this is only the PI for tablets and oral suspension.
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 lwoffii*
- *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 method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

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

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>
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*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

For testing *Neisseria gonorrhoeae*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.06</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>0.12 – 0.5</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 1</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>ATCC 29212</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>ATCC 49226</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 29213</td>
</tr>
</tbody>
</table>
This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).

This quality control range is applicable to only *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 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:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-20</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>=21</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

For testing *Neisseria gonorrhoeae*:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 11</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>28 – 40</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤27</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

Pursuant to Peter Dionne’s comments dated 6/29/00

Delete pursuant to Peter Dionne’s comments dated 6/29/00
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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>ATCC 25922</td>
</tr>
<tr>
<td>H. influenza&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ATCC 49247</td>
</tr>
<tr>
<td>N. gonorrhoeae&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ATCC 49226</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>ATCC 27853</td>
</tr>
<tr>
<td>S. aureus</td>
<td>ATCC 25923</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> 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.

3. INDICATIONS AND USAGE
   • As we requested, the order of the following indications was revised as follows:

   **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*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

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

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

Reorganized the order of the indications. No text has been added or deleted.

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

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

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

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

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

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii*, *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*.

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

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.² (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.

4. PRECAUTIONS

- The following paragraph was deleted in the Drug Interactions subsection to be consistent with other quinolone labeling:

5. ADVERSE REACTIONS

- The following sentence was moved from the fourth paragraph to the first paragraph which now reads:

- The following adverse events were added and this subsection now reads:

**BODY AS A WHOLE:** foot pain
CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis
CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia (See above.) (See PRECAUTIONS.)
GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.
HEMIC/LYMPHATIC: lymphadenopathy
MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout
RENAL/URETHERAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain
RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptyis, bronchospasm, pulmonary embolism
SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.) Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See WARNINGS.)
SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste

• In the Post-Marketing Adverse Events subsection, the following paragraph was added to replace the list of adverse events that previously existed (to be consistent with other quinolone labeling):

  Change in serum phenytoin, postural hypotension, vasculitis, agitation, confusion, delirium, dysphagia, myoclonus, nystagmus, toxic psychosis, constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time, myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture, albuminuria, candiduria, renal calculi, vaginal candidiasis, anaphylactic reactions, erythema, multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, anosmia, taste loss, and elevation of serum triglycerides, cholesterol, blood glucose, or serum potassium. (See PRECAUTIONS.)

6. OVERDOSE
• The following sentence was moved from the end of this section and is now the paragraph:

  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.

7. DOSAGE AND ADMINISTRATION
• The following text was deleted from this section and a sentence was added since the Dosage Guidelines Table incorporates the same information:

  Cipro Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table.
The following sentences were moved from the end to the beginning of this section and now appear before the Dosage Guidelines table. The last two paragraphs were combined into one as follows:

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 Dosage Guidelines table was revised to mirror the new revised order of indications as follows:

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

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit. For a discussion of ciprofloxacin serum concentrations in various human populations, see INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.

*The following sentence and table was added after the Dosing Guidelines table:

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

<table>
<thead>
<tr>
<th>Cipro Oral Dosage</th>
<th>Equivalent Cipro I.V Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg Tablet q 12 h</td>
<td>200 mg I.V. q 12 h</td>
</tr>
<tr>
<td>500 mg Tablet q 12 h</td>
<td>400 mg I.V. q 12 h</td>
</tr>
<tr>
<td>750 mg Tablet q 12 h</td>
<td>400 mg I.V. q 8 h</td>
</tr>
</tbody>
</table>

*The following instructions for Cipro Oral Suspension were moved to Instructions To The Pharmacist For Use/Handling Of CIPRO – Oral Suspension:
See Instructions for USE/HANDLING.

The second sentence under **Impaired Renal Function** was revised as follows:

These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment.

8. HOW SUPPLIED

The paragraph and table concerning Cipro Oral Suspension were revised as follows:

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.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Total volume after reconstitution</th>
<th>Ciprofloxacin Concentration</th>
<th>Ciprofloxacin contents per bottle</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>100 mL</td>
<td>250 mg/5 mL</td>
<td>5,000 mg</td>
<td>0026-8551-36</td>
</tr>
<tr>
<td>10%</td>
<td>100 mL</td>
<td>500 mg/5 mL</td>
<td>10,000 mg</td>
<td>0026-8553-36</td>
</tr>
</tbody>
</table>

9. As we agreed, the **CLINICAL STUDIES** section was deleted as follows:
10. Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension

The following information was moved/added to the beginning of this section:

CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g 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:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>250-mg</td>
<td>5 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>500-mg</td>
<td>10 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>750-mg</td>
<td>15 mL</td>
<td>7.5 mL</td>
</tr>
</tbody>
</table>

• The following sentence was moved to this section:

**CIPRO**: 5% and 10% Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

• The following sentence was revised to read:

11. PATIENT INFORMATION ABOUT
CIPRO® (ciprofloxacin hydrochloride) TABLETS
CIPRO (ciprofloxacin) 5% and 10% ORAL SUSPENSION

• This new section was added as follows:

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

What is CIPRO?

CIPRO is an antibiotic. It kills many kinds of bacteria that can cause infections of the bladder, kidney, prostate, cervix, stomach, intestines, lungs, sinus, bone, and skin. CIPRO has been shown in many clinical trials to be effective in the treatment of bacterial infections. As with all antibiotics, CIPRO is not effective in treating infections caused by viruses, such as the common cold or the flu. You should contact your doctor if you think your condition is not improving while taking CIPRO.

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).
How and when should I take CIPRO?

CIPRO Tablets:
Unless directed otherwise by your physician, CIPRO should be taken twice a day, at approximately the same time, in the morning and in the evening. (milk). You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

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.

Who should not take CIPRO?
You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as “quinolones”.

In general, CIPRO is not recommended.

What are the possible side effects of CIPRO?
CIPRO is generally well-tolerated. The most common side effects caused by CIPRO, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort.

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

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

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.
What about other medications I am taking?

Some antacids and multivitamins can interfere with the absorption of CIPRO and may prevent it from working. You should take CIPRO either 2 hours before or 6 hours after taking products that contain aluminum, calcium, iron, magnesium, or zinc.

Tell your health care provider if you are taking any theophylline products before starting CIPRO. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO. Inform your health care professional of all medications you're taking.

Remember:

- Take your dose of CIPRO in the morning and in the evening.
- Complete the course of CIPRO even if you are feeling better.
- Keep CIPRO and all medications out of reach of children.
- Do not give CIPRO to anyone other than the person for which it was prescribed.
- This information does not take the place of discussions with your doctor or health care professional about your medication or treatment.

Rx Only
PX##### 6/01 Bay o 9867 5202-2-A-U.S.-10 © 2001 Bayer Corporation XXXX
CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.

Cipro IV Label
The approved package insert for NDA 19-847 (IV in vials) and NDA 19-857 (IV in 5% dextrose) dated August, 2000 was electronically compared to the proposed draft labeling dated June 29, 2001, received July 2, 2001. The changes were as follows:

1. DESCRIPTION
"Latex-free" was added to the following sentence to read:

"The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride."

2. CLINICAL PHARMACOLOGY
- As we requested, new subheadings were added to this section and existing information was reorganized under the following: Absorption, Distribution, Metabolism, Excretion and Special Populations.
- The following paragraph concerning probenecid was deleted since the same information is stated in Drug Interactions:
The following paragraph was added to read:

"Drug-drug Interactions: 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 PRECAUTIONS: Drug Interactions.)"

The Microbiology subsection was revised as follows:

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
Citrobacter diversus Morganella morganii
Citrobacter freundii Proteus mirabilis
Enterobacter cloacae Proteus vulgaris
Escherichia coli Providencia rettgeri
Haemophilus influenzae Providencia stuartii
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*
*Aeromonas hydrophila*
*Campylobacter jejuni*
*Edwardsiella tarda*
*Enterobacter aerogenes*
*Klebsiella oxytoca*
*Legionella pneumophila*
*Neisseria gonorrhoeae*
*Pasteurella multocida*
*Salmonella enteritidis*

*Salmonella typhi*
*Shigella boydii*
*Shigella dysenteriae*
*Shigella flexneri*
*Shigella sonnei*
*Vibrio cholerae*
*Vibrio parahaemolyticus*
*Vibrio vulnificus*
*Yersinia enterocolitica*

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

Susceptibility Tests

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

For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*;

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*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*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>ATCC 29212</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 29213</td>
</tr>
</tbody>
</table>

*This quality control range is applicable to only* *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).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-\(\mu\)g 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-\(\mu\)g ciprofloxacin disk should be interpreted according to the following criteria:

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-20</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

\(^a\)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*\(^b\):

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>＞21</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

\(^b\)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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 25923</td>
</tr>
</tbody>
</table>

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

3. INDICATIONS AND USAGE
• The Lower Respiratory Infections statement was revised to read:

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

• The references to DOSAGE AND ADMINISTRATION in the Complicated intra-Abdominal Infections and Empirical Therapy for Febrile Neutropenic Patients statements were deleted since this reference appears at the beginning of this section.

4. CLINICAL STUDIES
• The following demographic information for Empirical Therapy for Febrile Neutropenic Patients was deleted for brevity:
5. PRECAUTIONS

• The Information for Patients subsection was revised to read:

**Information For Patients:** Patients should be advised:

- 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 ciprofloxacin may cause dizziness and lightheadedness:

- 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.

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

- 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.

• The following two statements were moved from the CLINICAL PHARMACOLOGY section and added to the Drug Interactions subsection:

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

  "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 ½ hour and 1.18 μg/mL between 6-8 hours after the end of infusion."

• At the end of the Drug Interactions subsection the following statement was deleted to be consistent with other quinolone labeling. It is also not a drug interaction:
6. ADVERSE REACTIONS

The following sentence was moved up to the first paragraph and is now the last sentence in that paragraph:

"Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."

The following events were moved to the third paragraph to the "additional events" table for consistency:

"HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time"

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

The following post-marketing adverse events were changed from table format to paragraph format to be consistent with other quinolone labeling and for brevity as follows:

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:

change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tendinitis/tendon rupture, vaginal candidiasis (See PRECAUTIONS.)
7. **DOSAGE AND ADMINISTRATION**

- This section was completely revised as follows:

CIPRO® I.V. should be administered 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.
<table>
<thead>
<tr>
<th>Infection</th>
<th>Type or Severity</th>
<th>Unit Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract</td>
<td>Mild/Moderate</td>
<td>200 mg</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>Lower Respiratory Tract</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td>Nosocomial Pneumonia</td>
<td>Mild/Moderate/Severe</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td>Skin and Skin Structure</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td>Bone and Joint</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td>Intra-Abdominal*</td>
<td>Complicated</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>Acute Sinusitis</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>Empirical Therapy in Febrile Neutropenic Patients</td>
<td>Ciprofloxacin</td>
<td>400 mg</td>
<td>q8h</td>
</tr>
<tr>
<td></td>
<td>+ Piperacillin</td>
<td>50 mg/kg</td>
<td>q4h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not to exceed 24 g/day</td>
<td></td>
</tr>
<tr>
<td>Inhalational anthrax (post-exposure)**</td>
<td>Adult</td>
<td>400 mg</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>10 mg/kg</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per dose, not to exceed 400 mg per dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Usual Duration

7-14 Days
7-14 Days
7-14 Days
7-14 Days
10-14 Days
7-14 Days
7-14 Days
≥ 4-6 Weeks
≥ 4-6 Weeks
7-14 Days
10 Days
28 Days
7-14 Days
60 Days
60 Days

*Added Usual Duration Column to table and removed Daily Dose column
**Added to be consistent between oral and I.V. PIs regarding Anthrax
* 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. For a discussion of ciprofloxacin serum concentrations in various human populations, see Inhalational Anthrax – Additional Information. Total duration of ciprofloxacin administration (IV 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.

(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.)

<table>
<thead>
<tr>
<th>Equivalent AUC Dosing Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRO Oral Dosage</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>250 mg Tablet q 12 h</td>
</tr>
<tr>
<td>500 mg Tablet q 12 h</td>
</tr>
<tr>
<td>750 mg Tablet q 12 h</td>
</tr>
</tbody>
</table>

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

Impaired Renal Function: The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

<table>
<thead>
<tr>
<th>Recommended Starting and Maintenance Doses for Patients with Impaired Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Clearance (mL/min)</td>
</tr>
</tbody>
</table>
>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:

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.

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

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

8. HOW SUPPLIED

- The second and third sentences in the first paragraph were revised to read:

"The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:

**VIAL:** manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220."

On November 14, 2001, an internal team meeting was held with Nancy Ostrove in DDMAC to discuss her proposed Patient Package Insert (PPI) for Cipro Tablets and Oral Solution (as requested by Dr. Sandy Kweder in response to the Anthrax crisis in the USA) and the PPI proposed by Bayer in June, 2001. It was decided that Dr. Eileen Navarro, Medical Officer would mesh the two proposed PPIs and draft an FDA response to Bayer. Once Dr. Rigo Roca, Medical Team Leader and Dr. Renata Albrecht, Acting Division Director concurred, the proposed FDA revisions would be faxed to Bayer. A fax with the following FDA revised PPI was sent to Bayer on January 14, 2002:

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. If your doctor has prescribed CIPRO

**What is CIPRO?**

CIPRO is an antibiotic.
CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?
CIPRO Tablets:
Unless directed otherwise by your physician, CIPRO should be taken twice a day, at approximately the same time, in the morning and in the evening.

CIPRO 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.

Who should not take CIPRO?
You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones".

CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant, or plan to become pregnant while taking CIPRO,

In general, CIPRO is not recommended

What are the possible side effects of Cipro?

Cipro is generally well tolerated. The most common side effects caused by CIPRO, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort.

. If you develop hives, difficulty breathing, or other symptoms of an allergic
reaction. If you develop a skin rash, you should stop taking CIPRO and call your health care professional.

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

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

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

What about other medications I am taking?

Cipro can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline or ________

Remember:

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

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

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

Keep CIPRO and all medications out of reach of children.

On December 18, 2001 an internal team meeting was held with Dr. Kathleen Uhl, Medical Officer, CDER Pregnancy Labeling Team, to discuss revised pregnancy labeling for Cipro. Bayer had been informed in November, 2001 that the Agency would like to strengthen the current pregnancy labeling and would be forwarding proposed labeling revisions in the near future. In addition, the company was notified of two other comments from Dr. Navarro and Dr. Roca concerning Cipro labeling. A fax with the following proposed labeling revisions was sent to Bayer on December 19, 2001:

1. PRECAUTIONS, Information for Patients
"Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption."

2. PRECAUTIONS
Please replace the current wording with the following:

**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.
cc:
HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca
HFD-590/MO/E. Navarro
HFD-590/D. Matecka
HFD-590/Micro/P. Dionne
HFD-590/PM/J. Saliba
K. Uhl/MO CDER Pregnancy Labeling Team

Concurrence:
HFD-590/ActingDivDir/R. Albrecht 1/30/01
HFD-590/MedTL/R. Roca 1/30/02
HFD-590/MO/E. Navarro 1/30/02

Robin Anderson, RN, MBA
Regulatory Review Officer

Eileen Navarro, MD
Medical Officer

APPEARS THIS WAY
ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robin Anderson
1/31/02 08:49:08 AM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 1/30/02.

Renata Albrecht
1/31/02 03:33:27 PM
MEDICAL OFFICER

APPEARS THIS WAY ON ORIGINAL
Labeling, Clinical and Chemistry Review #2 of Supplemental Labeling Revisions (SLRs) Review of Bayer’s Response to January 31, 2002 Approvable Letters:

Amendments Reviewed:

<table>
<thead>
<tr>
<th>Product</th>
<th>NDA #</th>
<th>SLR #</th>
<th>Letter Date</th>
<th>Receipt Date</th>
<th>Completed Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRO® (ciprofloxacin) Tablets, 100 mg, 250 mg, 500 mg, 750 mg</td>
<td>19-537</td>
<td>041</td>
<td>February 28, 2002</td>
<td>March 1, 2002</td>
<td>April 12, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) Oral Suspension, 5% and 10%, 250 mg, 500 mg</td>
<td>20-780</td>
<td>011</td>
<td>February 28, 2002</td>
<td>March 1, 2002</td>
<td>April 12, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 1% Solution in vials, 200 mg, 400 mg</td>
<td>19-847</td>
<td>026</td>
<td>February 28, 2002</td>
<td>March 1, 2002</td>
<td>April 12, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 0.2% Solution in 5% Dextrose in flexible containers, 200 mg, 400 mg</td>
<td>19-857</td>
<td>028</td>
<td>February 28, 2002</td>
<td>March 1, 2002</td>
<td>April 12, 2002</td>
</tr>
<tr>
<td>CIPRO® (ciprofloxacin) IV 0.2% Solution in 0.9% NaCl in flexible containers, 200 mg, 400 mg (never launched)</td>
<td>19-858</td>
<td>022</td>
<td>February 28, 2002</td>
<td>March 1, 2002</td>
<td>April 12, 2002</td>
</tr>
</tbody>
</table>

• FDA approvable letter for NDA 19-537/S-041 and NDA 20-780/S-011 dated January 31, 2002
• FDA fax to Bayer with labeling comments for February 28, 2002 submission dated March 21, 2002

Sponsor: Bayer Corporation Pharmaceutical Division

Background:
In December 2000/January 2001 Bayer submitted the labeling supplements noted above for prior approval (see Labeling and Clinical Review of these supplemental applications dated January 31, 2002). These SLRs provided for multiple changes to the Cipro package inserts in order to be more consistent with current labeling standards. The length was shortened to "make the package insert more physician friendly while maintaining all pertinent and required information." Microbiology labeling changes proposed by Peter Dionne, Microbiology Reviewer and faxed to the company on June 29, 2000 were also included in these submissions. A new Patient Information section (PPI) was also added to the Cipro oral formulation label. During labeling negotiations, FDA also recommended updated pregnancy labeling revisions.

On January 31, 2002, two approvable letters were sent to Bayer for the labeling supplements noted above (one for the Cipro oral label and one for the Cipro IV label). Bayer responded with a counterproposal for pregnancy labeling and the patient package insert (PPI) in an amendment submitted to the Cipro NDAs on February 28, 2002, received March 1, 2002.

On March 19, 2002 the FDA Cipro review team met to discuss the February 28, 2002 submission. The following comments were faxed to Bayer on March 21, 2002:
CIPRO Tablets and CIPRO IV Labels

• In the DESCRIPTION section, please revise the USP statement to read:

  Does not comply with USP— with regards to “loss on drying” and “residue on ignition”.

Note: Exceptions must be explicitly listed.

• In the PRECAUTIONS section, Pregnancy subsection, please delete the words '___' in the following sentence:

  Note: The endpoint ‘___’ is poorly defined and it is a term that ACOG recommends not be used. Its appearance in the summary/labeling is misleading.

CIPRO Tablet Label Only

• In the CLINICAL STUDIES section, we agree that the sinusitis study may be removed, but please keep the UTI study information. The information that this section communicates is important in helping physicians to make a dosage regimen selection.

A revised label incorporating the FDA comments noted above was sent to the Division on March 27, 2002 for Cipro IV label and April 1, 2002 for Cipro oral label. The UTI study wording for the Cipro oral label had been negotiated via e-mail with Andrew Verderame at Bayer on March 27, 2002, and the wording that the Division recommended was included in the revised label.

Electronic Labeling Comparison

Cipro Oral Formulation:
The last approved label dated August 30, 2000 was electronically compared to the proposed draft label dated April 1, 2002. The changes were as follows:

Double underline—added
Strikethrough—deleted

1. DESCRIPTION
• The description of tablet color and the addition of "corn" to the word "starch" were added as follows:
Ciprofloxacin tablets are white to slightly yellowish. CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg The inactive ingredients are corn starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

• The following sentence was added to the end of this section to read:

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

2. CLINICAL PHARMACOLOGY

• As we requested, new subheadings were added to this section and existing information was reorganized under the following: Absorption, Distribution, Metabolism, Excretion and Special Populations.

• Under Absorption, the following sentence was added and is now the third sentence in the second paragraph:

The serum elimination half-life in subjects with normal renal function is approximately 4 hours.

• The Microbiology subsection was revised as follows:

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 iwoffii*  
*Pasteurella multocida*  
*Aeromonas hydrophila*  
*Salmonella enteritidis*  
*Edwardsiella tarda*  
*Vibrio cholerae*  
*Enterobacter aerogenes*  
*Vibrio parahaemolyticus*  
*Klebsiella oxytoca*  
*Vibrio vulnificus*  
*Legionella pneumophila*  
*Yersinia enterocolitica*

Reviewer Note: “Acinetobacter Iwoffii” is spelled incorrectly in the list above. There should be one i, not two.

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

---

**Susceptibility Tests**

**Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.

Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

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

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:
MIC (µg/mL)  
≤ 1  
0.12 - 0.5  
≥ 1  

Interpretation  
Susceptible (S)  
Intermediate (I)  
Resistant (R)

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

For testing *Neisseria gonorrhoeae*:

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>ATCC 29212</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>ATCC 49226</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 29213</td>
</tr>
</tbody>
</table>

This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).
This quality control range is applicable to only *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 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-μg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae, and Neisseria gonorrhoeae*:\n
<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-20</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:\n
<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

For testing *Neisseria gonorrhoeae*:\n
<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥36</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>28 - 40</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤27</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>ATCC 25922</td>
</tr>
<tr>
<td>H. influenza</td>
<td>ATCC 49247</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>ATCC 49226</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>ATCC 27853</td>
</tr>
<tr>
<td>S. aureus</td>
<td>ATCC 25923</td>
</tr>
</tbody>
</table>

\[^a\] These quality control limits are applicable to only H. influenza 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.

3. INDICATIONS AND USAGE

As we requested, the order of the following indications was revised as follows:

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

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

Chronic Bacterial Prostatitis caused by Escherichia coli or Proteus mirabilis.

Lower Respiratory Tract Infections caused by Escherichia coli, Klebsiella pneumoniae, Enterobacter cloaceae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, or Streptococcus pneumoniae. Also, Moraxella catarrhalis for the treatment of acute exacerbations of chronic bronchitis.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

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

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

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

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

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

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

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

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

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

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.° (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 CIPRC 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.

4. PRECAUTIONS

• The first bullet under Information for Patients was revised to read:

  ♦ 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, 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 dairy products (like milk or with 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.

**REVIEWER NOTE:** This wording was not previously discussed with Bayer, but in an e-mail message dated March 20, 2002, Dr. Joette Meyer, Biopharmaceutics Reviewer stated that she agreed with the Bayer's proposed wording.

• The following paragraph was deleted in the Drug Interactions subsection to be consistent with other quinolone labeling:

**The Pregnancy: Teratogenic Effects. Pregnancy Category C subsection was revised to read:**

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). 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 less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see WARNINGS).

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

• The following sentence was added to the Nursing Mothers subsection and is now the second sentence:

"The amount of ciprofloxacin absorbed by the nursing infant is unknown."

5. ADVERSE REACTIONS
• The first paragraph in this section was revised to read:

During clinical investigation with the tablet, 2,799 patients received 2,868 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 3.5% of patients treated.

• The following adverse events were added to this subsection:
BODY AS A WHOLE: foot pain

HEMIC/LYMPHATIC: lymphadenopathy

• The following sentence was deleted after the list of additional events:

• The following paragraph was deleted (was the fourth paragraph in this section):

• In the Post-Marketing Adverse Events subsection, the following paragraph was added to replace the table of adverse events that previously existed (to be consistent with other quinolone labeling):

  agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia, hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), vaginal candidiasis, and vasculitis (See PRECAUTIONS.)

6. OVERDOSAGE
• The following sentence was moved and is now the last sentence in this section:

  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.

7. DOSAGE AND ADMINISTRATION
• This section was completely revised and now reads:

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

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

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

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

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
** Drug administration should begin as soon as possible after suspected or confirmed exposure.
This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit. For a discussion of ciprofloxacin serum concentrations in various human populations, see INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.

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

<table>
<thead>
<tr>
<th>Cipro Oral Dosage</th>
<th>Equivalent Cipro I.V Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg Tablet q 12 h</td>
<td>200 mg I.V. q 12 h</td>
</tr>
<tr>
<td>500 mg Tablet q 12 h</td>
<td>400 mg I.V. q 12 h</td>
</tr>
<tr>
<td>750 mg Tablet q 12 h</td>
<td>400 mg I.V. q 8 h</td>
</tr>
</tbody>
</table>

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

A. **RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>See Usual Dosage.</td>
</tr>
<tr>
<td>30 - 50</td>
<td>250-500 mg q 12 h</td>
</tr>
<tr>
<td>5 - 29</td>
<td>250-500 mg q 18 h</td>
</tr>
<tr>
<td>Patients on hemodialysis</td>
<td>250-500 mg q 24 h (after dialysis)</td>
</tr>
<tr>
<td>or Peritoneal dialysis</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Women: \(0.85 \times\) the value calculated for men.

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

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

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

8. **HOW SUPPLIED**

• The paragraph and table concerning Cipro Oral Suspension were revised as follows:

  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.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Total volume after reconstitution</th>
<th>Ciprofloxacin Concentration</th>
<th>Ciprofloxacin contents per bottle</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>100 mL</td>
<td>250 mg/5 mL</td>
<td>5,000 mg</td>
<td>0026-8551-36</td>
</tr>
<tr>
<td>10%</td>
<td>100 mL</td>
<td>500 mg/5 mL</td>
<td>10,000 mg</td>
<td>0026-8553-36</td>
</tr>
</tbody>
</table>

9. As we agreed, the original CLINICAL STUDIES section was deleted and replaced by the following:

**Uncomplicated Cystitis**

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

10. **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral Suspension**

The following information was added to the beginning of this section:

CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g 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:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>250-mg</td>
<td>5 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>500-mg</td>
<td>10 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>750-mg</td>
<td>15 mL</td>
<td>7.5 mL</td>
</tr>
</tbody>
</table>
The following sentences were added to this section:

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.

Instructions To The Patient For Taking CIPRO - Oral Suspension was deleted since a new patient package insert has been added to the end of this label.

11. REFERENCES

The following references were added:


12. A new section called "PATIENT INFORMATION ABOUT CIPRO® (ciprofloxacin hydrochloride) TABLETS, CIPRO® (ciprofloxacin) ORAL SUSPENSION" was added to read:

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

What is CIPRO?

CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria that can infect these areas of the body. CIPRO has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your condition is not improving while taking CIPRO.
CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:

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

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

CIPRO Oral Suspension:

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

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as “quinolones”.

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

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

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

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

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

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

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

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

**What about other medications I am taking?**

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

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

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

CIPRO has been approved to reduce the chance of developing anthrax infection following exposure to the anthrax bacteria. In general, CIPRO is not recommended for children; however, it is approved for use in patients younger than 18 years old for anthrax exposure. If you are pregnant, or plan to become pregnant while taking CIPRO, you and your doctor should discuss if the benefits of taking CIPRO for anthrax outweigh the risks.
CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent anthrax might be acceptable due to the seriousness of the disease. You and your doctor should discuss the risks of not taking your medicine against the risks of experiencing side effects.

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

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

Remember:

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

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

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

Keep CIPRO and all medications out of reach of children.

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516 USA

Rx Only

PX##### 3/02 Bay o 9867 5202-2-A-U.S.-10  © 2002 Bayer Corporation XXXX

CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.

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

Cipro IV Formulation:
The last approved label dated August 30, 2000 was electronically compared to the proposed draft label dated March 27, 2002. The changes were as follows:

Double underline = added
Strike through = deleted

1. DESCRIPTION
• The following sentence was deleted from the second paragraph in this section:
"Latex-free" was added to the following sentence to read:

"The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride."

2. CLINICAL PHARMACOLOGY

- As we requested, new subheadings were added to this section and existing information was reorganized under the following: Absorption, Distribution, Metabolism, Excretion and Special Populations.

- The following paragraph concerning probenecid was deleted since the same information is stated in Drug Interactions:

- The following paragraph was added to read:

"Drug-drug Interactions: The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonlurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See PRECAUTIONS: Drug Interactions.)"

- The Microbiology subsection was revised as follows:

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**
- *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 Iwoffii*  
*Aeromonas hydrophila*  
*Campylobacter jejuni*  
*Edwardsiella tarda*  
*Enterobacter aerogenes*  
*Klebsiella oxytoca*  
*Legionella pneumophila*  
*Neisseria gonorrhoeae*  
*Pasteurella multocida*  
*Salmonella enteritidis*

*Salmonella typhi*  
*Shigella boydii*  
*Shigella dysenteriae*  
*Shigella flexneri*  
*Shigella sonnei*  
*Vibrio cholerae*  
*Vibrio parahaemolyticus*  
*Vibrio vulnificus*  
*Yersinia enterocolitica*

**Reviewer Note:** "*Acinetobacter Iwoffii*" is spelled incorrectly in the list above. There should be one *i*, not two.

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 aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

\(^a\)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*:\(^b\):

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

\(^b\)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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>ATCC 29212</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 29213</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥21</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-20</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>
These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

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

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 21</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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

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

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>ATCC 25922</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>ATCC 49247</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>ATCC 27853</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>ATCC 25923</td>
</tr>
</tbody>
</table>

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

- The Lower Respiratory Infections statement was revised to read:

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

- The references to DOSAGE AND ADMINISTRATION in the Complicated intra-Abdominal Infections and Empirical Therapy for Febrile Neutropenic Patients statements were deleted since this reference appears at the beginning of this section.

4. CLINICAL STUDIES

- The following demographics information for Empirical Therapy for Febrile Neutropenic Patients was deleted for brevity:

5. WARNINGS

- There is a typographical error in the word "have" in the following statement that should be noted as a minor editorial correction in the approval letter:

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)
6. PRECAUTIONS

• The Information for Patients subsection was revised to read:

  **Information For Patients**: Patients should be advised:

  • 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 ciprofloxacin may cause dizziness and lightheadedness;

  • 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.

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

  • 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.

• The following two statements were moved from the **CLINICAL PHARMACOLOGY** section and added to the **Drug Interactions** subsection:

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

  "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 ½ hour and 1.18 µg/mL between 6-8 hours after the end of infusion."

• At the end of the **Drug Interactions** subsection the following statement was deleted to be consistent with other quinolone labeling. It is also not a drug interaction:
•The Pregnancy: Teratogenic Effects. Pregnancy Category C subsection was revised to read:

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.  

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 less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see WARNINGS).

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

•The following sentence was added to the Nursing Mothers subsection and is now the second sentence:
"The amount of ciprofloxacin absorbed by the nursing infant is unknown."

7. ADVERSE REACTIONS
• The following sentence was moved and is now the last sentence in the first paragraph:

"Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment."

• The following events were moved from the third paragraph to the "additional events" table for consistency:

"HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time"

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

• The following post-marketing adverse events were changed from table format to paragraph format to be consistent with other quinolone labeling and for brevity as follows:

**Post-Marketing Adverse Events:** Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tendonitis/tendon rupture, vaginal candidiasis (See PRECAUTIONS.)

8. DOSAGE AND ADMINISTRATION
• This section was completely revised. The new text reads as follows:

**CIPRO® L.V.** should be administered by intravenous infusion over a period of 60 minutes. 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 L.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.
### DOSAGE GUIDELINES

<table>
<thead>
<tr>
<th>Infection</th>
<th>Type or Severity</th>
<th>Unit Dose</th>
<th>Frequency</th>
<th>Usual Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract</td>
<td>Mild/Moderate</td>
<td>200 mg</td>
<td>q12h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q12h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td>Respiratory Tract</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q6h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td>Nosocomial Pneumonia</td>
<td>Mild/Moderate/Severe</td>
<td>400 mg</td>
<td>q6h</td>
<td>10-14 Days</td>
</tr>
<tr>
<td>Skin and Skin Structure</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q6h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td>Bone and Joint</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
<td>≥ 4-6 Weeks</td>
</tr>
<tr>
<td></td>
<td>Severe/Complicated</td>
<td>400 mg</td>
<td>q6h</td>
<td>≥ 4-6 Weeks</td>
</tr>
<tr>
<td>Intra-Abdominal</td>
<td>Complicated</td>
<td>400 mg</td>
<td>q12h</td>
<td>7-14 Days</td>
</tr>
<tr>
<td>Acute Sinusitis</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
<td>10 Days</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>Mild/Moderate</td>
<td>400 mg</td>
<td>q12h</td>
<td>28 Days</td>
</tr>
</tbody>
</table>

**Empirical Therapy in Febrile Neutropenic Patients**
- **Ciprofloxacin**: 400 mg q8h, 7-14 Days
- **Piperacillin**: 50 mg/kg, not to exceed 4000 mg/day

**Inhalational anthrax (post-exposure)**
- **Adult**: 400 mg q12h, 60 Days
- **Pediatric**: 10 mg/kg per dose, not to exceed 400 mg per dose, 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. For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.** Total duration of ciprofloxacin administration (IV 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.**

**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

<table>
<thead>
<tr>
<th>CIPRO Oral Dosage</th>
<th>Equivalent CIPRO I.V. Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg Tablet q 12 h</td>
<td>200 mg I.V. q 12 h</td>
</tr>
<tr>
<td>500 mg Tablet q 12 h</td>
<td>400 mg I.V. q 12 h</td>
</tr>
<tr>
<td>750 mg Tablet q 12 h</td>
<td>400 mg I.V. q 8 h</td>
</tr>
</tbody>
</table>

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

**Impaired Renal Function:** The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

### RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>See usual dosage.</td>
</tr>
<tr>
<td>5-29</td>
<td>200-400 mg q 18-24 hr</td>
</tr>
</tbody>
</table>

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

Men: Creatinine clearance (mL/min) = Weight (kg) x (140 - age) x 72 x serum creatinine (mg/dL)

Women: 0.85 x the value calculated for men.

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

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

### 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

9. HOW SUPPLIED
The third and fourth sentences in the first paragraph were revised to read:

"The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:
VIAL: manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220."

10. STORAGE
The following USP statement was added to the end of this section:

"Ciprofloxacin is also available as CIPRO (ciprofloxacin HCl) Tablets 100, 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”.

10. REFERENCES
The following references were added:


Conclusions/Recommendations:
The labeling changes proposed by Bayer are acceptable. Two approval letters (one for Cipro Tablets/Oral Suspension and one for the CIPRO IV formulations) should be sent advising the applicant that these NDA labeling supplements are approved. The Cipro Tablet/Oral Solution letter should include the minor editorial correction noted in the patient package insert. The Cipro IV approval letter should include the minor editorial correction noted in WARNINGS.

Robin Anderson, R.N., M.B.A.
Regulatory Review Officer

Eileen Navarro, M.D.
Medical Officer

Dorota Matecka, Ph.D.
Chemistry Reviewer

cc: HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca
HFD-590/OE/N. Navarro
HFD-590/Chem/D. Matecka
HFD-590/ChemTL/N. Schmuff
HFD-590/Biopharm/J. Meyer
HFD-590/BiopharmTL/B. Davit
HFD-590/Micro/P. Dionne
HFD-590/MicroTL/S. Bala
HFD-590/PM/J. Saliba

Concurrence:
HFD-590/ActingDivDir/R. Albrecht 4/17/02
HFD-590/MedTL/R. Roca 4/17/02
HFD-590/OE/E. Navarro 4/16/02
HFD-590/Chem/D. Matecka 4/17/02
HFD-590/ChemTL/N. Schmuff 4/16/02
HFD-590/Biopharm/J. Meyer 4/16/02
HFD-590/BiopharmTL/B. Davit 4/16/02
HFD-590/Micro/P. Dionne 4/16/02
HFD-590/MicroTL/S. Bala 4/16/02
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robin Anderson
4/17/02 11:29:02 AM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 4/17/02.

Renata Albrecht
4/17/02 05:09:19 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL
MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDAs #: 19-537/SLR-041
20-780/SLR-011
REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 22-DEC-00
CDER DATE: 26-DEC-00
REVIEW ASSIGN DATE: 08-JAN-01
REVIEW COMPLETE DATE: 01-FEB-01

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON: Andrew S. Verderame
Associate Director, Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Labeling amendment—changes to Microbiology subsection

DRUG CATEGORY: Antimicrobial: Fluoroquinolone


DOSAGE FORM: 100-mg, 250-mg, 500-mg and 750-mg Tablets; 5% and 10% Oral Suspension

DRUG PRODUCT NAME
PROPRIETARY: CIPRO® Tablets and Oral Suspension
NONPROPRIETARY/USAN: ciprofloxacin hydrochloride and ciprofloxacin
CODE: BAY q 3939
CHEMICAL NAME: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[1-piperazinyl]-3-quinolone-carboxylic acid

STRUCTURAL FORMULA:

Molecular Formula: C_{17}H_{15}FN_{2}O_{3}
Molecular Weight: 331.4
Reviewer’s Comments: These revisions were recommended to the sponsor in the June 29, 2000 facsimile and make the label more consistent with other quinolone labeling. Information about the activity being less when tested at acidic pH and about the MBC generally being 2 times the MIC has been moved from lines 263-266 to lines 174-176. These changes in the ciprofloxacin label will make it more consistent with other antibacterial labels.

In line 171 the words “In vitro” should be in italics.

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)

Staphylococcus epidermidis (methicillin-susceptible)

Staphylococcus saprophyticus

Streptococcus pneumoniae (penicillin-susceptible)

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni

Citrobacter diversus

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Salmonella typhi

Serratia marcescens

Shigella boydii

Shigella dysenteriae

Shigella flexneri

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

Reviewer’s Comments: Staphylococcus aureus and Staphylococcus epidermidis in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of (methicillin-susceptible). Streptococcus pneumoniae in line 195 should be qualified as (penicillin-susceptible strains) instead of (penicillin-susceptible).

The deletion of the _______________ s appears to be acceptable. This will make the package insert shorter and may eliminate confusion since very few if any other labels have two clinical efficacy listings. Most of the organisms are the same in both listings except for Neisseria gonorrhoeae and organisms associated with infectious diarrhea and typhoid fever which the I.V. formulation is not approved for. _______________ does not cause a problem since no organisms will be moved to the in vitro only listing. _______________ will have additional organisms added to the in vitro listing which will not be associated with infections for which the I.V. formulation is approved. This does not seem to be a real problem, however, since the oral formulations are approved for these organisms and the I.V. label already has Vibrio species and Yersinia enterocolitica included.
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* (underscored)

Aerobic gram-negative microorganisms
- *Acinetobacter Iwofii*
- *Aeromonas hydrophila*
- *Edwardsiella tarda*
- *Enterobacter aerogenes*
- *Klebsiella oxytoca*
- *Legionella pneumophila*
- *Pasteurella multocida*
- *Salmonella enteritidis*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Vibrio vulnificus*
- *Yersinia enterocolitica*

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

Reviewer's Comments: *Streptococcus pneumoniae* in line 249 should be qualified as (penicillin-resistant strains) instead of *Streptococcus pneumoniae*. The deletion of the last paragraph (lines 263-266) is acceptable since this information has been moved to the introduction of the Microbiology subsection (lines 174-176).

Susceptibility Tests

Reviewer's Comments: The only revisions to the Susceptibility Tests is the addition of Intermediate and Resistant criteria to both the Dilution Techniques and Diffusion Techniques for the testing of *Neisseria gonorrhoeae*, the revision of the zone diameter susceptible criteria for *Neisseria gonorrhoeae* and

All these revisions are acceptable.
CONCLUSIONS:

With a few minor revisions the changes made to the Microbiology subsection of the package insert are acceptable. These revisions are indicated below in the Recommendations section as notification to the sponsor.

RECOMMENDATIONS:

The sponsor should be notified of the following:

1. In line 171 the words In vitro should be in italic in the sentence that begins "In vitro resistance to ciprofloxacin develops slowly ..."

2. *Staphylococcus aureus* and *Staphylococcus epidermidis* in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of (methicillin-susceptible).

3. *Streptococcus pneumoniae* in lines 195 and 249 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of (penicillin-susceptible) and (penicillin-resistant)

All other revisions to the Microbiology subsection are acceptable.

________________________________________
Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir __________________ Signature ______________ Date

HFD-590/TLMicro __________________ Signature ______________ Date

CC:

HFD-590/Original NDA #19-537/SLR-041
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/EO/ENavarro
HFD-590/Chem/DMatecka
HFD-590/CSO/VJensen
HFD-590/CSO/RAnderson

APPEARS THIS WAY ON ORIGINAL
/s/
-------------
Peter Dionne
2/21/01 09:12:05 AM
MICROBIOLOGIST

Shukal signed 2/1/2001 Ken signed 2/9/2001

Shukal Bala
2/21/01 10:28:11 AM
MICROBIOLOGIST

Kenneth Hastings
2/21/01 02:27:45 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL
MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDAs #: 19-537/SLR-041 20-780/SLR-011
REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 22-JUN-01
CDER DATE: 25-JUN-01
REVIEW ASSIGN DATE: 29-JUN-01
REVIEW COMPLETE DATE: 02-JUL-01

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON: Robin M. Christoforides
Assistant Director, Regulatory Affairs
Phone Number: (203) 812-2112

SUBMISSION REVIEWED: Labeling amendment—changes to Microbiology subsection

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Urinary Tract Infections, Cystitis in females, Prostatitis, Lower Respiratory
Tract Infections, Sinusitis, Skin and Skin Structure Infections, Bone and
Joint Infections, Complicated Intra-Abdominal Infections, Infectious
Diarrhea, Typhoid Fever, Gonorrhea, Inhalational Anthrax (post-exposure)

DOSAGE FORM: 100-mg, 250-mg, 500-mg and 750-mg Tablets; 5% and 10% Oral
Suspension

DRUG PRODUCT NAME

PROPRIETARY: CIPRO® Tablets and Oral Suspension
NONPROPRIETARY/USAN: ciprofloxacin hydrochloride and ciprofloxacin
CODE: BAY q 3939
CHEMICAL NAME: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[1-piperazinyl]-
3-quinolone-carboxylic acid

STRUCTURAL FORMULA:

Molecular Formula: C_{17}H_{16}F_{N_{3}}O_{3}
Molecular Weight: 331.4
BACKGROUND:

This is a labeling supplement. In this supplement the sponsor has revised the labeling for ciprofloxacin tablets and oral suspension to make the package insert more consistent with current labeling standards and to shorten the length of the label.

Bayer also acknowledges receipt of a facsimile dated March 5, 2001 that includes comments on these supplements that were submitted December 22, 2000. These submissions are Bayer’s response to the Division’s comments. Bayer has included a revised proposed label.

The microbiology comments and the sponsor’s response to each are stated below.

1. In line 171 the words In vitro should be in italic in the sentence that begins “In vitro resistance to ciprofloxacin develops slowly …

The words “In vitro” have been italicized. Refer to line 182 in the revised proposed labeling.

2. \textit{Staphylococcus aureus} and \textit{Staphylococcus epidermidis} in lines 192 and 193 should be qualified as (methicillin-susceptible strains only) instead of (methicillin-susceptible).

\textit{Staphylococcus aureus} and \textit{Staphylococcus epidermidis} have been qualified as (methicillin-susceptible strains only). Refer to lines 203 and 204 in the revised proposed labeling.

3. \textit{Streptococcus pneumoniae} in lines 195 and 249 should be qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the label instead of .

\textit{Streptococcus pneumoniae} has been qualified as (penicillin-susceptible strains) and (penicillin-resistant strains) in the appropriate sections of the revised label. Refer to lines 206 and 260 in the revised proposed labeling.
CONCLUSIONS:

The Microbiology subsection of the label is now acceptable.

RECOMMENDATIONS:

All revisions to the Microbiology subsection are acceptable.

APPEARS THIS WAY ON ORIGINAL

__________________________
Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_________________Signature_____________Date
HFD-590/TLMicro_________________Signature_____________Date

CC:
HFD-590/Original NDA #19-537/SLR-041; NDA #20-780/SLR-011
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ENavarro
HFD-590/Chem/DMatecka
HFD-590/Pharm/SHundley
HFD-590/CSO/JSaliba
HFD-590/CSO/RAnderson
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Peter Dionne
7/11/01 09:29:24 AM
MICROBIOLOGIST

Shukal signed off 7/6/01  Ken signed 7/9/01

Shukal Bala
7/11/01 09:45:27 AM
MICROBIOLOGIST

Kenneth Hastings
7/24/01 10:05:55 AM
PHARMACOLOGIST

APPEARS THIS WAY ON ORIGINAL
APPLICATION NUMBER:

19-537/S-041
20-780/S-011

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE
NDA 19-537/S-041  
NDA 20-780/S-011  

PRIOR APPROVAL SUPPLEMENT

Bayer Corporation Pharmaceutical Division  
Attention: Andrew S. Verderame  
Associate Director, Regulatory Affairs  
400 Morgan Lane  
West Haven, CT 06516-4175

Dear Mr. Verderame:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>Supplement Number</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-537</td>
<td>S-041</td>
<td>CIPRO (ciprofloxacin hydrochloride) tablets</td>
</tr>
<tr>
<td>20-780</td>
<td>S-011</td>
<td>CIPRO (ciprofloxacin) oral suspension</td>
</tr>
</tbody>
</table>

Date of Supplements: December 22, 2000

Date of Receipt: December 26, 2000

These supplemental applications, submitted as "Supplement - Changes Being Effected" supplements, propose the following change(s):

- Addition of Patient Information section
- Revision of Microbiology section

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on February 24, 2001 in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:
U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Valerie Jensen, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
/s/

Ellen Frank
1/29/01 07:00:22 PM
NDA 19-537/S-041 & NDA 20-780/S-011

APPEARS THIS WAY
ON ORIGINAL