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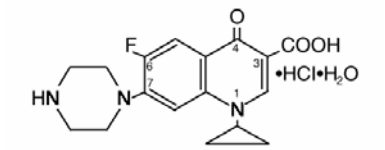
CIPRO® XR
(ciprofloxacin* extended-release tablets)

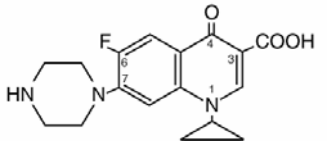
Revised Proposed PI **08/29/03**

DESCRIPTION

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



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



• 3.5 H_2O

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

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

CLINICAL PHARMACOLOGY

Absorption

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

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher than the corresponding BID doses, while the AUCs over 24 hours are equivalent.

The following table compares the pharmacokinetic parameters obtained at steady state for these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin immediate-release).

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

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

§ median (range)

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

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours

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after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

Elimination

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See **PRECAUTIONS, Geriatric Use.)**

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO XR should be reduced to CIPRO XR 500 mg q 24 h in patients with creatinine clearance below 30 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

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In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **DOSAGE AND ADMINISTRATION.**)

Drug-drug Interactions

Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc. (See **PRECAUTIONS, Drug Interactions and Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

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

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

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents

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such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to $1x10^{-6}$.

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

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

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus saprophyticus

Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

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

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

Aerobic gram-negative microorganisms
Citrobacter koseri
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

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

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procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to the following criteria:

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

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

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

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

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

Acute Uncomplicated Pyelonephritis caused by *Escherichia coli*.

[a] Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO XR may be initiated before results of these tests are

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known; once results become available appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO XR 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 CIPRO XR IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

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

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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."

If a diagnosis of pseudomembranous colitis is 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.

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.**)

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

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quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

Information for Patients:

Patients should be advised:

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

- if the patient should forget to take CIPRO XR at the usual time, he/she may take the dose later in the day. Do not take more than one CIPRO XR tablet per day even if a patient misses a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**.

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

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

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

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

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

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

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 interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Absorption of the CIPRO XR tablet was slightly diminished (20%) when given concomitantly with omeprazole. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions.)**

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

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

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

Quinolones 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.

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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 V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

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

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

Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2 and 3 -fold greater than the 1000 mg daily human dose based upon body surface area).
Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to the maximum recommended daily human dose of 1000 mg based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.

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

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (1.0 times the highest recommended daily human dose of 1000 mg based upon body surface area) revealed no evidence of impairment.

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

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures). There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

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

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.7 and 0.4 times the maximum daily human dose of 1000 mg based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

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

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whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use: In a large, prospective, randomized CIPRO XR clinical trial in complicated urinary tract infections, 49% (509/1035) of the patients were 65 and over, while 30% (308/1035) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and clinical experience with other formulations of ciprofloxacin has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTATION.**)

ADVERSE REACTIONS

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

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

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyleonephritis, CIPRO XR (1000 mg once daily) in 517 patients was compared to ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7 to 14 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 3.1% (16/517) of patients in the CIPRO XR arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the CIPRO XR arm were

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nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

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

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

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

BODY AS A WHOLE: abdominal pain, asthenia, malaise, photosensitivity reaction
CARDIOVASCULAR: bradycardia, migraine, syncope
DIGESTIVE: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst
HEMIC/LYMPHATIC: prothrombin decreased
CENTRAL NERVOUS SYSTEM: abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo
METABOLIC: hyperglycemia
SKIN/APPENDAGES: dry skin, maculopapular rash, pruritus, rash, skin disorder, urticaria, vesiculobullous rash
SPECIAL SENSES: diplopia, taste perversion
UROGENITAL: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide post-marketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications). Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure. The events are:
achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions), anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, flushing, gastrointestinal bleeding, gout (flare up), gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic necrosis, hiccup, hyperpigmentation, hypertension, hypotension, ileus, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lymphadenopathy, manic

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reaction, myalgia, myasthenia gravis (possible exacerbation), myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, paranoia, paresthesia, perspiration (increased), phobia, pleural effusion, polyuria, postural hypotension, pseudomembranous colitis, pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, Stevens-Johnson syndrome, tachycardia, taste loss, tendinitis, tendon rupture, tinnitus, toxic epidermal necrolysis, toxic psychosis, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

Laboratory Changes:

The following adverse laboratory changes, in alphabetical order, regardless of incidence or relationship to drug, have been reported in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications):

Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts, prothrombin time, serum albumin, serum potassium, total serum protein, uric acid.

Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving theophylline concomitantly), serum triglycerides, uric acid.

Others: albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs, leukocytosis, methemoglobinemia, pancytopenia.

OVERDOSAGE

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

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

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent

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species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

DOSAGE AND ADMINISTRATION

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

DOSAGE GUIDELINES

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

Patients whose therapy is started with CIPRO I.V. for urinary tract infections may be switched to CIPRO XR when clinically indicated at the discretion of the physician.

CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO XR may be taken with meals that include milk, concomitant administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. A 2-hour window between substantial calcium intake (> 800 mg) and dosing with CIPRO XR is recommended. CIPRO XR should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions**, **PRECAUTIONS, Drug Interactions and Information for Patients**.)

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Impaired Renal Function:

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

Impaired Hepatic Function:

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

HOW SUPPLIED

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

	Strength	NDC Code
Bottles of 50	500 mg	0026-8889-50
Bottles of 100	500 mg	0026-8889-51
Bottles of 50	1000 mg	0026-8897-50
Bottles of 100	1000 mg	0026-8897-51
Unit Dose Pack of 30	1000 mg	0026-8897-69

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

ANIMAL PHARMACOLOGY

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

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

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

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

CLINICAL STUDIES

Uncomplicated Urinary Tract Infections (acute cystitis)

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

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

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

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

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

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

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

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

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

The Per Protocol population was defined as patients with a diagnosis of cUTI or AUP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, no inclusion criteria violation, a valid test-of-cure urine culture within the TOC window, an organism susceptible to study drug, no premature discontinuation or loss to follow-up, and compliance with the dosage regimen (among other criteria). More patients in the CIPRO XR arm than in the control arm were excluded from the Per Protocol population and this should be considered in the interpretation of the study results. Reasons for exclusion with the greatest discrepancy between the two arms were no valid test of cure urine culture, an organism resistant to the study drug, and premature discontinuation due to adverse events.

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

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

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

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

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

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

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

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

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

Of the 166 cUTI patients treated with CIPRO XR, 148 (89%) had the causative organism(s) eradicated, 8 (5%) had persistence, 5 (3%) patients developed superinfections and 5 (3%) developed new infections. Of the 177 cUTI patients treated in the control arm, 144 (81%) had the causative organism(s) eradicated, 16 (9%) patients had persistence, 3 (2%) developed superinfections and 14 (8%) developed new infections. Of the 40 patients with AUP treated with CIPRO XR, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had

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persistence and 3 (7.5%) developed new infections. Of the 5 CIPRO XR AUP patients without eradication at TOC, 4 were considered clinical cures and did not receive alternative antibiotic therapy. Of the 52 patients with AUP treated in the control arm, 51 (98%) had the causative organism(s) eradicated. One patient (2%) had persistence.

References: 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003.
2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

PATIENT INFORMATION ABOUT CIPRO® XR (ciprofloxacin extended-release tablets)

This section contains important patient information about CIPRO XR 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 XR. CIPRO XR can be prescribed only by a licensed health care professional. Your doctor has prescribed CIPRO XR only for you.

CIPRO XR is intended only to treat urinary tract infections and acute uncomplicated pyelonephritis (also known as a kidney infection). It should not be used to treat other infections. Do not give it to other people even if they have a similar condition. Do not use it for a condition for which it was not prescribed. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO XR is right for you.

What is CIPRO XR?

CIPRO XR is an antibiotic in the quinolone class that contains the active ingredient ciprofloxacin. CIPRO XR is specifically formulated to be taken just once daily to kill bacteria causing infection in the urinary tract. CIPRO XR has been shown in clinical trials to be effective in the treatment of urinary tract infections. You should contact your doctor if your condition is not improving while taking CIPRO XR.

CIPRO XR Tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. CIPRO XR is available in ~~a~~ 500 mg and 1000 mg tablet strengths.

How and when should I take CIPRO XR?

CIPRO XR should be taken once a day for three (3) to fourteen (14) days depending on your infection. Take CIPRO XR at approximately the same time each day with food or on an empty stomach. CIPRO XR should not be taken with dairy products (like milk or yogurt) or

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calcium-fortified juices alone; however, CIPRO XR may be taken with a meal that contains these products. Should you forget to take it at the usual time, you may take your dose later in the day. Do not take more than one CIPRO XR tablet per day even if you missed a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET**.

You should take CIPRO XR 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.

Who should not take CIPRO XR?

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

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

CIPRO XR is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO XR?

CIPRO XR is generally well tolerated. The most common side effects, which are usually mild, include nausea, headache, dyspepsia, dizziness, vaginal yeast infection and diarrhea. If diarrhea persists, call your health care professional. Antibiotics of the quinolone class may also cause vomiting, rash, and abdominal pain/discomfort.

You should be careful about driving or operating machinery until you are sure CIPRO XR is not causing dizziness.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including ciprofloxacin, 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 XR 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 XR.

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

Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions. Quinolones, including ciprofloxacin, have been

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rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

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 XR can affect how other medicines work. Tell your doctor about all other prescriptions and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline or VIDEX® (didanosine) chewable/buffered tablets or pediatric powder. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO XR.

Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO XR and may prevent it from working. You should take CIPRO XR either 2 hours before or 6 hours after taking these products.

Remember:

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

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

Keep CIPRO XR and all medications out of reach of children.

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

Rx Only

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