

**CIPROFLOXACIN- ciprofloxacin hydrochloride tablet, film coated, extended release**  
**Dr. Reddy's Laboratories Limited**

**Ciprofloxacin Extended-Release Tablets**

**BOXED WARNING**

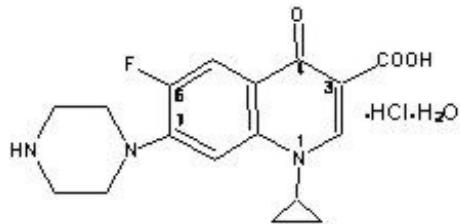
**WARNING: Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung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

**Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis (see WARNINGS).**

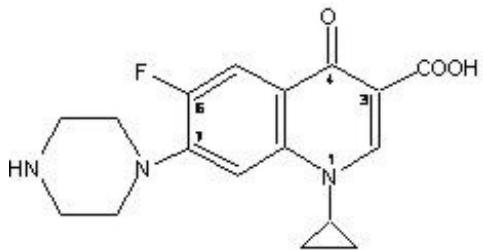
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin extended-release tablets and other antibacterial drugs, ciprofloxacin extended-release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by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

**DESCRIPTION**

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



Ciprofloxacin, USP is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. As the anhydrous form, its empirical formula is  $C_{17}H_{18}FN_3O_3$  and its molecular weight is 331.34. It is a pale yellowish to light yellow crystalline substance and its chemical structure is as follows:



Ciprofloxacin extended-release tablets are available in 500 mg and 1000 mg (ciprofloxacin equivalent) tablet strength. Ciprofloxacin extended-release tablets are white to off white, film coated, oblong shaped, biconvex tablets. Each ciprofloxacin extended-release 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on anhydrous basis) and ciprofloxacin (212.6 mg, calculated on the dried basis) Each ciprofloxacin extended-release 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on anhydrous basis) and ciprofloxacin (425.2 mg, calculated on the dried basis). The inactive ingredients are crospovidone, colloidal silicon dioxide, ethylcellulose, hypromellose, magnesium stearate, polyethylene glycol, succinic acid and titanium dioxide

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<sup>1</sup> as ciprofloxacin and ciprofloxacin hydrochloride

## CLINICAL PHARMACOLOGY

### Absorption

Ciprofloxacin extended-release 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 ciprofloxacin extended-release tablets. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-release BID treatment, the  $C_{max}$  of ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets versus 250 mg BID ciprofloxacin immediate-release tablets and 1000 mg QD ciprofloxacin extended-release tablets versus 500 mg BID ciprofloxacin immediate-release).

### Ciprofloxacin Pharmacokinetics (Mean $\pm$ SD) Following Ciprofloxacin Tablets and Ciprofloxacin Extended-Release Tablets Administration

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

\* median (range)

Results of the pharmacokinetic studies demonstrate that ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58 mg/L for the 1000 mg tablet.

## Metabolism

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

## Elimination

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

ciprofloxacin extended-release tablets. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of ciprofloxacin extended-release tablets should be reduced to ciprofloxacin extended-release tablets 500 mg q24h in patients with creatinine clearance below 30 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

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

## **Drug-Drug Interactions**

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

### **Antacids**

When ciprofloxacin extended-release tablets given as a single 1000 mg dose was administered two hours before, or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean  $C_{max}$  of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets 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**

### **Mechanism of Action**

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.

**Drug Resistance** The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, microorganisms resistant to these classes of 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<sup>-9</sup> to 1x10<sup>-6</sup>.

## Activity in vitro and in vivo

Ciprofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. 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 ciprofloxacin extended-release tablets..

### 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 ( $\geq$  90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin extended-release tablets in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

### Aerobic gram-negative microorganisms

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

## Susceptibility Tests

- Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to the criteria outlined in Table 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<sup>2</sup> 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 criteria outlined in Table 1. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

**Table 1: Susceptibility Interpretive Criteria for Ciprofloxacin**

Species	MIC ( $\mu\text{g/mL}$ )			Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	$\leq 1$	2	$\geq 4$	$\geq 21$	16-20	$\leq 15$
Enterococcus faecalis	$\leq 1$	2	$\geq 4$	$\geq 21$	16-20	$\leq 15$
Pseudomonas aeruginosa	$\leq 1$	2	$\geq 4$	$\geq 21$	16-20	$\leq 15$
Staphylococcus saprophyticus	$\leq 1$	2	$\geq 4$	$\geq 21$	16-20	$\leq 15$

S=Susceptible, I=Intermediate, and R=Resistant.

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.

- **Quality Control:** 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 according to criteria outlined in Table 2. For the diffusion technique, the 5- $\mu\text{g}$  ciprofloxacin disk should provide the zone diameters outlined in Table 2.

**Table 2: Quality Control for Susceptibility Testing**

Strains	MIC range ( $\mu\text{g/mL}$ )	Zone Diameter (mm)
Enterococcus faecalis ATCC 29212	0.25-2	-
Escherichia coli ATCC 25922	0.004-0.015	30-40
Pseudomonas aeruginosa ATCC 27853	0.25-1.0	25-33
Staphylococcus aureus ATCC29212	0.12-0.5	-
Staphylococcus aureus ATCC25923	-	22-30

## INDICATIONS AND USAGE

Ciprofloxacin extended-release tablets are indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms as listed below. Ciprofloxacin extended-release tablets 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*<sup>2</sup>.

**Complicated Urinary Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*<sup>2</sup>.

**Acute Uncomplicated Pyelonephritis** caused by *Escherichia coli*.

**THE SAFETY AND EFFICACY OF CIPROFLOXACIN EXTENDED-RELEASE TABLETS 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 ciprofloxacin extended-release tablets may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

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

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<sup>2</sup> Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

## CONTRAINdications

Ciprofloxacin extended-release tablets are contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

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

## WARNINGS

### Tendinopathy and Tendon Rupture:

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

**Exacerbation of Myasthenia Gravis:** Fluoroquinolones, including ciprofloxacin extended-release tablets, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid ciprofloxacin extended-release tablets in patients with known history of myasthenia gravis. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS: Post-Marketing Adverse Event Reports**).

**THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN EXTENDED-RELEASE TABLETS 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 **ANIMALPHARMACOLOGY.**)

### **Cytochrome P450 (CYP450)**

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

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

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

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

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.**)

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

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

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

## **Peripheral Neuropathy**

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

## **PRECAUTIONS**

### **General**

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

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

### **Photosensitivity/Phototoxicity**

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

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

### **Information for Patients**

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue ciprofloxacin extended-release tablets treatment. The risk of severe tendon disorder with

fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

- that fluoroquinolones like ciprofloxacin extended-release tablets may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.
- that antibacterial drugs including ciprofloxacin extended-release tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ciprofloxacin extended-release tablets is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ciprofloxacin extended-release tablets or other antibacterial drugs in the future.
- that ciprofloxacin extended-release tablets may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration with magnesium/aluminum antacids, or sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or with other products containing calcium, iron, or zinc should be avoided. Ciprofloxacin extended-release tablets 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**.) Ciprofloxacin extended-release tablets 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 extended-release tablets 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 ciprofloxacin extended-release tablets at the usual time, he/she may take the dose later in the day. Do not take more than one ciprofloxacin extended-release tablet per day even if a patient misses a dose. Swallow the ciprofloxacin extended-release 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 ciprofloxacin extended-release tablets at the first sign of a skin rash or other allergic reaction.
- that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.
- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- that ciprofloxacin extended-release tablets may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.
- that ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets if there is a history of

this condition.

- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

## Drug Interactions

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

Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

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

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

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for Patients, and DOSAGE AND ADMINISTRATION**.)

Histamine H<sub>2</sub>-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

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

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

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

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

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

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

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

carefully monitored when concomitant ciprofloxacin therapy is indicated.

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

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

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

Salmonella/Microsome Test (Negative)

*E. coli* DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V<sub>79</sub> 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<sup>2</sup>), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.

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

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

### **Pregnancy**

#### **Teratogenic Effects**

#### *Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial

teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state there is no risk.

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

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

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

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

## **Nursing Mothers**

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

## **Pediatric Use**

Safety and effectiveness of ciprofloxacin extended-release tablets in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

## **Geriatric Use**

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as ciprofloxacin extended-release tablets. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing ciprofloxacin extended-release tablets to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue ciprofloxacin extended-release tablets and contact their healthcare provider

if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning, WARNINGS, and ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

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

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

## **ADVERSE REACTIONS**

Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500 mg or 1000 mg ciprofloxacin extended-release tablets. 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 ciprofloxacin extended-release tablets. 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, ciprofloxacin extended-release tablets (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 ciprofloxacin extended-release tablets arm and in 0% (0/447) of patients in the control arm.

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyelonephritis, ciprofloxacin extended-release tablets (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 ciprofloxacin extended-release tablets arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the ciprofloxacin extended-release tablets arm were nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

In these clinical trials, the following events occurred in  $\geq$  2% of all ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets treated patients were:

**Body As a Whole:** abdominal pain, asthenia, malaise, photosensitivity reaction

**Cardiovascular:** bradycardia, migraine, syncope

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

**Hemic/Lymphatic:** prothrombin decrease

**Central Nervous System:** abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

**Metabolic:** hyperglycemia

**Skin/Hypersensitivity:** dry skin, maculopapular rash, photosensitivity/phototoxicity reactions, pruritus, rash, skin disorder, urticaria, vesiculobullous rash

**Special Senses:** diplopia, taste perversion

**Urogenital:** dysmenorrhea, hematuria, kidney function abnormal, vaginitis

**Post-Marketing Adverse Event Reports:** The following adverse events have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure. The events in alphabetical order are:

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

## Laboratory Changes

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

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

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

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

## OVERDOSAGE

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

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

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

## DOSAGE AND ADMINISTRATION

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

### DOSAGE GUIDELINES

<u>Indication</u>	<u>Unit Dose</u>	<u>Frequency</u>	<u>Usual Duration</u>
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 ciprofloxacin I.V. for urinary tract infections may be switched to ciprofloxacin extended-release tablets when clinically indicated at the discretion of the physician.

Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets are recommended. Ciprofloxacin extended-release tablets should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.** (See **CLINICAL PHARMACOLOGY**, **Drug-drug Interactions**, **PRECAUTIONS**, **Drug Interactions** and **Information for Patients**.)

### **Impaired Renal Function**

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

### **Impaired Hepatic Function**

No dosage adjustment is required with ciprofloxacin extended-release tablets 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**

Ciprofloxacin extended-release tablets, 500 mg are white to off-white, film coated, oblong shaped, biconvex tablets, embossed with 'RDY' on one side and '422' on other side. They are supplied in bottles of 30's, 100's, 500's and unit-dose package of 100 (10×10).

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Bottles of 30	NDC 55111-422-30
Bottles of 100	NDC 55111-422-01
Bottles of 500	NDC 55111-422-05
Unit-dose package of 100 (10×10)	NDC 55111-422-78

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Ciprofloxacin extended-release tablets, 1000 mg are white to off-white, film coated, oblong shaped, biconvex tablets, embossed with 'RDY' on one side and '423' on other side. They are supplied in bottles of 30's, 100's, 500's and unit-dose packages of 100 (10×10).

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Bottles of 30	NDC 55111-423-30
Bottles of 100	NDC 55111-423-01
Bottles of 500	NDC 55111-423-05
Unit-dose package of 100 (10×10)	NDC 55111-423-78

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Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

### **ANIMAL PHARMACOLOGY**

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in

beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

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

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

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

## CLINICAL STUDIES

### Uncomplicated Urinary Tract Infections (acute cystitis)

Ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets (500 mg once daily for three days) with ciprofloxacin immediate-release tablets (ciprofloxacin 250 mg BID for three days). Of the 905 patients enrolled, 452 were randomly assigned to the ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (ciprofloxacin extended-release tablets minus control group) are given in the following table:

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

\* 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).

† 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

## **Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis**

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

An analysis of all patients with a causative organism(s) isolated at baseline and who received study medication, defined as the MITT population, included 342 patients in the ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets and control arm, respectively [97.5% CI<sup>3</sup> (-13.5%, 5.7%)]. Clinical cure was 184/271 (67.9%) for ciprofloxacin extended-release tablets and 182/248 (73.4%) for control arm, respectively [97.5% CI<sup>3</sup> (-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 ciprofloxacin extended-release tablets and control arm, respectively [97.5% CI<sup>3</sup> (-26.8%, 6.5%)]. Clinical cure at TOC was 50/71 (70.4%) for ciprofloxacin extended-release tablets and 58/76 (76.3%) for the control arm [97.5% CI<sup>3</sup> (-22.0%, 10.4%)].

In the Per Protocol population, the differences between ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets arm than in the control arm. For AUP patients, the bacteriologic eradication rate was lower in the ciprofloxacin extended-release tablets 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 ciprofloxacin extended-release tablets and the control arm, respectively.

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

	<b>CIPROFLOXACIN EXTENDED-RELEASE TABLETS 1000 mg QD</b>	<b>CIPROFLOXACIN TABLETS 500 mg BID</b>
Randomized Patients	521	521
Per Protocol Patients*	206	229
<b>cUTI Patients</b>		

Bacteriologic Eradication at TOC (n/N) <sup>†</sup>	148/166 (89.2%)	144/177 (81.4%)
CI [-0.7%, 16.3%]		
Bacteriologic Eradication (by organism) at TOC (n/N) <sup>‡</sup>		
<i>E. coli</i>	91/94 (96.8%)	90/92 (97.8%)
<i>K. pneumoniae</i>	20/21 (95.2%)	19/23 (82.6%)
<i>E. faecalis</i>	17/17 (100%)	14/21 (66.7%)
<i>P. mirabilis</i>	11/12 (91.6%)	10/10 (100%)
<i>P. aeruginosa</i>	3/3 (100%)	3/3 (100%)
Clinical Cure at TOC (n/N) <sup>§</sup>	159/166 (95.8%)	161/177 (91.0%)
CI [-1.1%, 10.8%]		
<b>AUP Patients</b>		
Bacteriologic Eradication at TOC (n/N) <sup>†</sup>	35/40 (87.5%)	51/52 (98.1%)
CI [-34.8%, 6.2%]		
Bacteriologic Eradication of <i>E. coli</i> at TOC (n/N) <sup>‡</sup>	35/36 (97.2%)	41/41 (100%)
Clinical Cure at TOC (n/N) <sup>§</sup>	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 ciprofloxacin extended-release tablets, 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 ciprofloxacin extended-release tablets, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had persistence and 3 (7.5%) developed new infections. Of the 5 ciprofloxacin extended-release tablets 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.

3 confidence interval of the difference in rates (ciprofloxacin extended-release tablets minus control).

## References

1. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth Edition. CLSI Document M7-A8, Vol. 29, No. 2, CLSI, Wayne, PA, January, 2009.
2. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – Tenth Edition. CLSI Document M2-A10, Vol. 29, No. 1, CLSI, Wayne, PA, January, 2009.

Manufactured by:

**Dr. Reddy's Laboratories Limited**

Bachepalli – 502 325 INDIA

Revised:0811

## **MEDICATION GUIDE**

### **CIPROFLOXACIN TABLETS, USP**

### **CIPROFLOXACIN EXTENDED-RELEASE TABLETS**

READ THE MEDICATION GUIDE THAT COMES WITH CIPROFLOXACIN TABLETS BEFORE YOU START TAKING IT AND EACH TIME YOU GET A REFILL. THERE MAY BE NEW INFORMATION. THIS MEDICATION GUIDE DOES NOT TAKE THE PLACE OF TALKING TO YOUR HEALTHCARE PROVIDER ABOUT YOUR MEDICAL CONDITION OR YOUR TREATMENT.

#### **What is the most important information I should know about ciprofloxacin tablets?**

CIPROFLOXACIN BELONGS TO A CLASS OF ANTIBIOTICS CALLED FLUOROQUINOLONES. CIPROFLOXACIN TABLETS CAN CAUSE SIDE EFFECTS THAT MAY BE SERIOUS OR EVEN CAUSE DEATH. IF YOU GET ANY OF THE FOLLOWING SERIOUS SIDE EFFECTS, GET MEDICAL HELP RIGHT AWAY. TALK WITH YOUR HEALTHCARE PROVIDER ABOUT WHETHER YOU SHOULD CONTINUE TO TAKE CIPROFLOXACIN TABLETS.

#### **1. Tendon rupture or swelling of the tendon (tendinitis)**

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

**rupture:**

- hear or feel a snap or pop in a tendon area
- bruising right after an injury in a tendon area
- unable to move the affected area or bear weight

## **2. WORSENING OF MYASTHENIA GRAVIS (A DISEASE WHICH CAUSES MUSCLE WEAKNESS).**

FLUOROQUINOLONES LIKE CIPROFLOXACIN MAY CAUSE WORSENING OF MYASTHENIA GRAVIS SYMPTOMS, INCLUDING MUSCLE WEAKNESS AND BREATHING PROBLEMS. CALL YOUR HEALTHCARE PROVIDER RIGHT AWAY IF YOU HAVE ANY WORSENING MUSCLE WEAKNESS OR BREATHING PROBLEMS.

SEE THE SECTION “**WHAT ARE THE POSSIBLE SIDE EFFECTS OF CIPROFLOXACIN TABLETS?**” FOR MORE INFORMATION ABOUT SIDE EFFECTS.

### **What are ciprofloxacin tablets ?**

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

Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking ciprofloxacin tablets.

Ciprofloxacin tablets should not be used as the first choice of antibiotic medicine in children under 18 years of age. Ciprofloxacin tablets should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if ciprofloxacin extended-release tablets are safe and works in children under 18 years of age.

SOMETIMES INFECTIONS ARE CAUSED BY VIRUSES RATHER THAN BY BACTERIA. EXAMPLES INCLUDE VIRAL INFECTIONS IN THE SINUSES AND LUNGS, SUCH AS THE COMMON COLD OR FLU. ANTIBIOTICS, INCLUDING CIPROFLOXACIN TABLETS, DO NOT KILL VIRUSES.

CALL YOUR HEALTHCARE PROVIDER IF YOU THINK YOUR CONDITION IS NOT GETTING BETTER WHILE YOU ARE TAKING CIPROFLOXACIN TABLETS.

### **Who should not take ciprofloxacin tablets ?**

DO NOT TAKE CIPROFLOXACIN TABLETS IF YOU:

- HAVE EVER HAD A SEVERE ALLERGIC REACTION TO AN ANTIBIOTIC KNOWN AS A FLUOROQUINOLONE, OR ARE ALLERGIC TO ANY OF THE INGREDIENTS IN CIPROFLOXACIN TABLETS. ASK YOUR HEALTHCARE PROVIDER IF YOU ARE NOT SURE. SEE THE LIST OF INGREDIENTS IN CIPROFLOXACIN TABLETS AT THE END OF THIS MEDICATION GUIDE.
- ALSO TAKE A MEDICINE CALLED TIZANIDINE (ZANAFLEX® ). SERIOUS SIDE EFFECTS FROM TIZANIDINE ARE LIKELY TO HAPPEN.

### **What should I tell my healthcare provider before taking ciprofloxacin tablets ?**

**SEE “WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT CIPROFLOXACIN TABLETS?”**

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

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems

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

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

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

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

**KNOW THE MEDICINES YOU TAKE. KEEP A LIST OF YOUR MEDICINES AND SHOW IT TO YOUR HEALTHCARE PROVIDER AND PHARMACIST WHEN YOU GET A NEW MEDICINE.**

**How should I take ciprofloxacin tablets?**

- Take ciprofloxacin tablets exactly as prescribed by your healthcare provider.

- Take ciprofloxacin tablets in the morning and evening at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you cannot swallow the tablet whole.
- Take ciprofloxacin extended-release tablets one time each day at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you cannot swallow the tablet whole.
- Ciprofloxacin tablets can be taken with or without food.
- Ciprofloxacin tablets should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking ciprofloxacin tablets.
- Do not skip any doses, or stop taking ciprofloxacin tablets even if you begin to feel better, until you finish your prescribed treatment, unless:
  - you have tendon effects (see “**What is the most important information I should know about ciprofloxacin tablets?**”),
  - you have a serious allergic reaction (see “**What are the possible side effects of ciprofloxacin tablets?**”), or
  - your healthcare provider tells you to stop.

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

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

#### **If you have been prescribed ciprofloxacin tablets after being exposed to anthrax:**

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

#### **What should I avoid while taking ciprofloxacin tablets?**

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

#### **What are the possible side effects of ciprofloxacin tablets?**

Ciprofloxacin tablets can cause side effects that may be serious or even cause death. See “**What is the most important information I should know about ciprofloxacin tablets?**”

OTHER SERIOUS SIDE EFFECTS OF CIPROFLOXACIN TABLETS INCLUDE:

- **Central Nervous System Effects**

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

**CENTRAL NERVOUS SYSTEM (CNS) SIDE EFFECTS MAY HAPPEN AS SOON AS AFTER TAKING THE FIRST DOSE OF CIPROFLOXACIN TABLETS. TALK TO YOUR HEALTHCARE PROVIDER RIGHT AWAY IF YOU GET ANY OF THESE SIDE EFFECTS, OR OTHER CHANGES IN MOOD OR BEHAVIOR:**

- feel dizzy
- seizures
- hear voices, see things, or sense things that are not there (hallucinations)
- feel restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- nightmares
- feel more suspicious (paranoia)
- suicidal thoughts or acts

- **Serious allergic reactions**

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

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- faint
- yellowing of the skin or eyes. Stop taking ciprofloxacin tablets and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to ciprofloxacin tablets (a liver problem).

- **Skin rash**

Skin rash may happen in people taking ciprofloxacin tablets, even after only one dose. Stop taking ciprofloxacin tablets at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to ciprofloxacin tablets.

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

- who are elderly
- with a family history of prolonged QT interval,

- with low blood potassium (hypokalemia),
  - who take certain medicines to control heart rhythm (antiarrhythmics).
- **Intestine infection** (Pseudomembranous colitis) Pseudomembranous colitis can happen with most antibiotics, including ciprofloxacin tablets. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy) Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including ciprofloxacin tablets. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
  - pain
  - burning
  - tingling
  - numbness
  - weakness

CIPROFLOXACIN TABLETS MAY NEED TO BE STOPPED TO PREVENT PERMANENT NERVE DAMAGE.

- **Low blood sugar (hypoglycemia)**

People who take ciprofloxacin tablets and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with ciprofloxacin tablets. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity)**

See “**What should I avoid while taking ciprofloxacin tablets?**”

- **Joint Problems**

Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child’s healthcare provider if your child has any joint problems during or after treatment with ciprofloxacin tablets.

THE MOST COMMON SIDE EFFECTS OF CIPROFLOXACIN TABLETS INCLUDE:

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

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF CIPROFLOXACIN TABLETS. TELL YOUR HEALTHCARE PROVIDER ABOUT ANY SIDE EFFECT THAT BOTHERS YOU, OR THAT DOES NOT GO AWAY.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO FDA AT 1-800-FDA-1088.

**How should I store ciprofloxacin tablets?**

- Ciprofloxacin Tablets:
  - Store ciprofloxacin tablets below 86°F (30°C).
- Ciprofloxacin Extended-Release Tablets:
  - Store ciprofloxacin extended-release tablets at 20°-25°C (68°-77°F); excursions permitted to

15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

**KEEP CIPROFLOXACIN TABLETS AND ALL MEDICINES OUT OF THE REACH OF CHILDREN.**

## **GENERAL INFORMATION ABOUT CIPROFLOXACIN TABLETS**

MEDICINES ARE SOMETIMES PRESCRIBED FOR PURPOSES OTHER THAN THOSE LISTED IN A MEDICATION GUIDE. DO NOT USE CIPROFLOXACIN TABLETS FOR A CONDITION FOR WHICH IT IS NOT PRESCRIBED. DO NOT GIVE CIPROFLOXACIN TABLETS TO OTHER PEOPLE, EVEN IF THEY HAVE THE SAME SYMPTOMS THAT YOU HAVE. IT MAY HARM THEM.

THIS MEDICATION GUIDE SUMMARIZES THE MOST IMPORTANT INFORMATION ABOUT CIPROFLOXACIN TABLETS. IF YOU WOULD LIKE MORE INFORMATION ABOUT CIPROFLOXACIN TABLETS, TALK WITH YOUR HEALTHCARE PROVIDER. YOU CAN ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST FOR INFORMATION ABOUT CIPROFLOXACIN TABLETS THAT IS WRITTEN FOR HEALTHCARE PROFESSIONALS. FOR MORE INFORMATION CALL 1-888-375-3784.

### **What are the ingredients in ciprofloxacin tablets?**

- Ciprofloxacin Tablets:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, sodium starch glycolate, corn starch and titanium dioxide.
- Ciprofloxacin Extended-Release Tablets:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: crospovidone, colloidal silicon dioxide, ethylcellulose, hypromellose, magnesium stearate, polyethylene glycol, succinic acid and titanium dioxide

To reorder additional medguides, please contact Dr. Reddy's Customer Service at 1-866-733-3952.

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

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Revised:0811

## **PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION**

500 mg Labels

Container label



100 Tablets

NDC 55111-422-01

**CIPROFLOXACIN  
Extended Release  
Tablets 500 mg**

Rx Only

PHARMACIST: PLEASE  
DISPENSE WITH  
MEDICATION GUIDE  
PROVIDED

**DESCRIPTION:** Each Ciprofloxacin\* Extended Release 500 mg tablet contains 500 mg of ciprofloxacin.

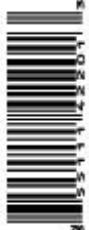
**USAGE:** See accompanying literature for complete information on dosage and administration.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

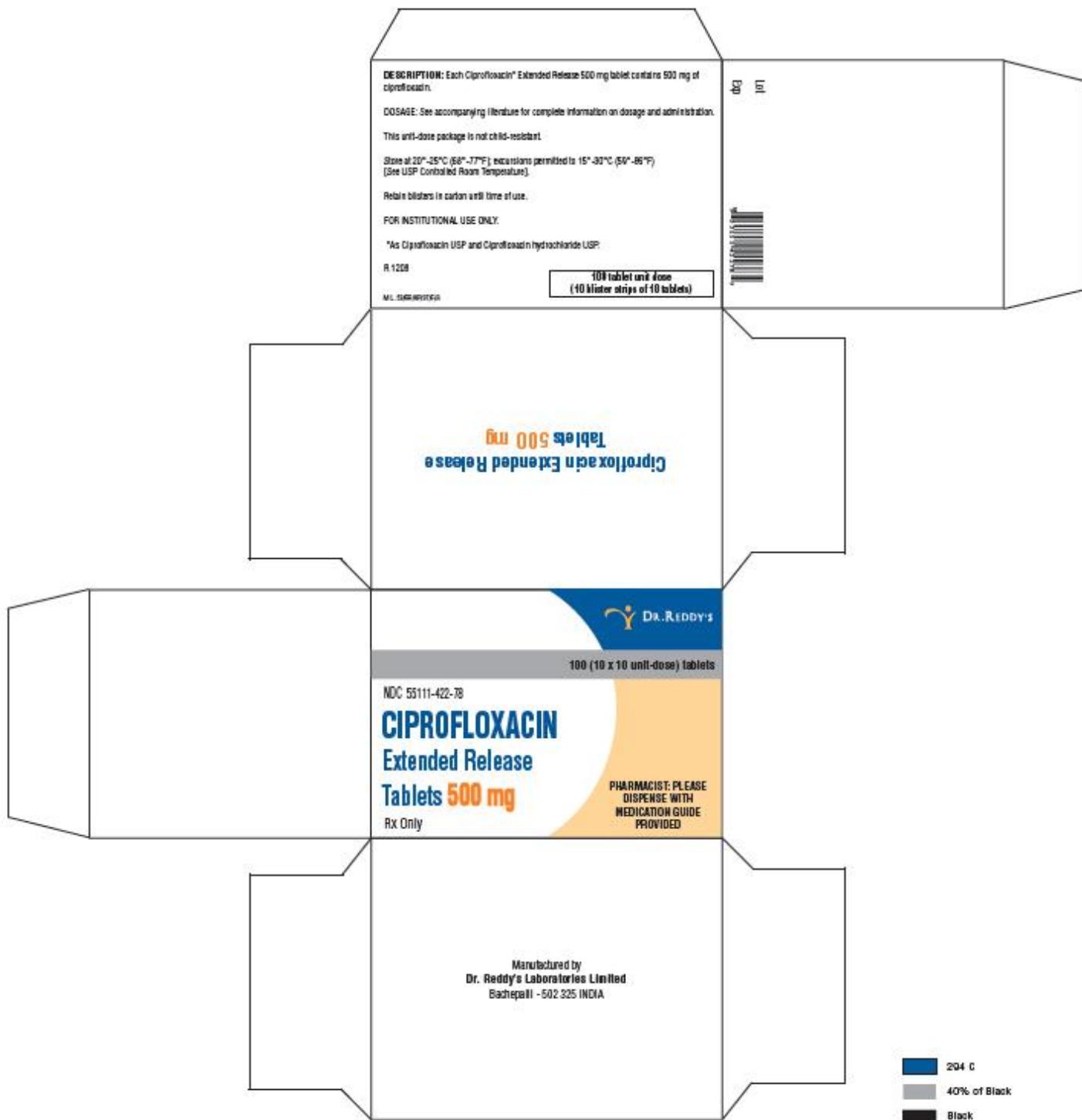
\*As Ciprofloxacin USP and Ciprofloxacin hydrochloride USP.

R 1208

Mfg. By: Dr. Reddy's Laboratories Limited  
Bachupalli - 502325 INDIA  
M.L. SURAPRASADAR

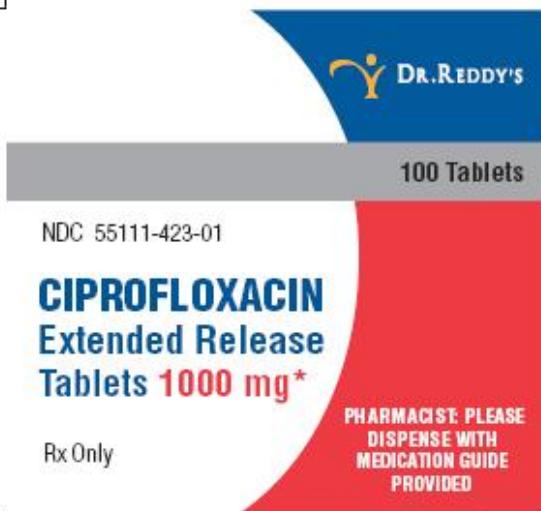


LOT  
EXP



## 1000 mg Labels

Container label



**DESCRIPTION:** Each Ciprofloxacin\* Extended Release 1000 mg tablet contains 1000 mg of ciprofloxacin.

**DOSAGE:** See accompanying literature for complete information on dosage and administration.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

\*As Ciprofloxacin USP and Ciprofloxacin hydrochloride USP.

R1208

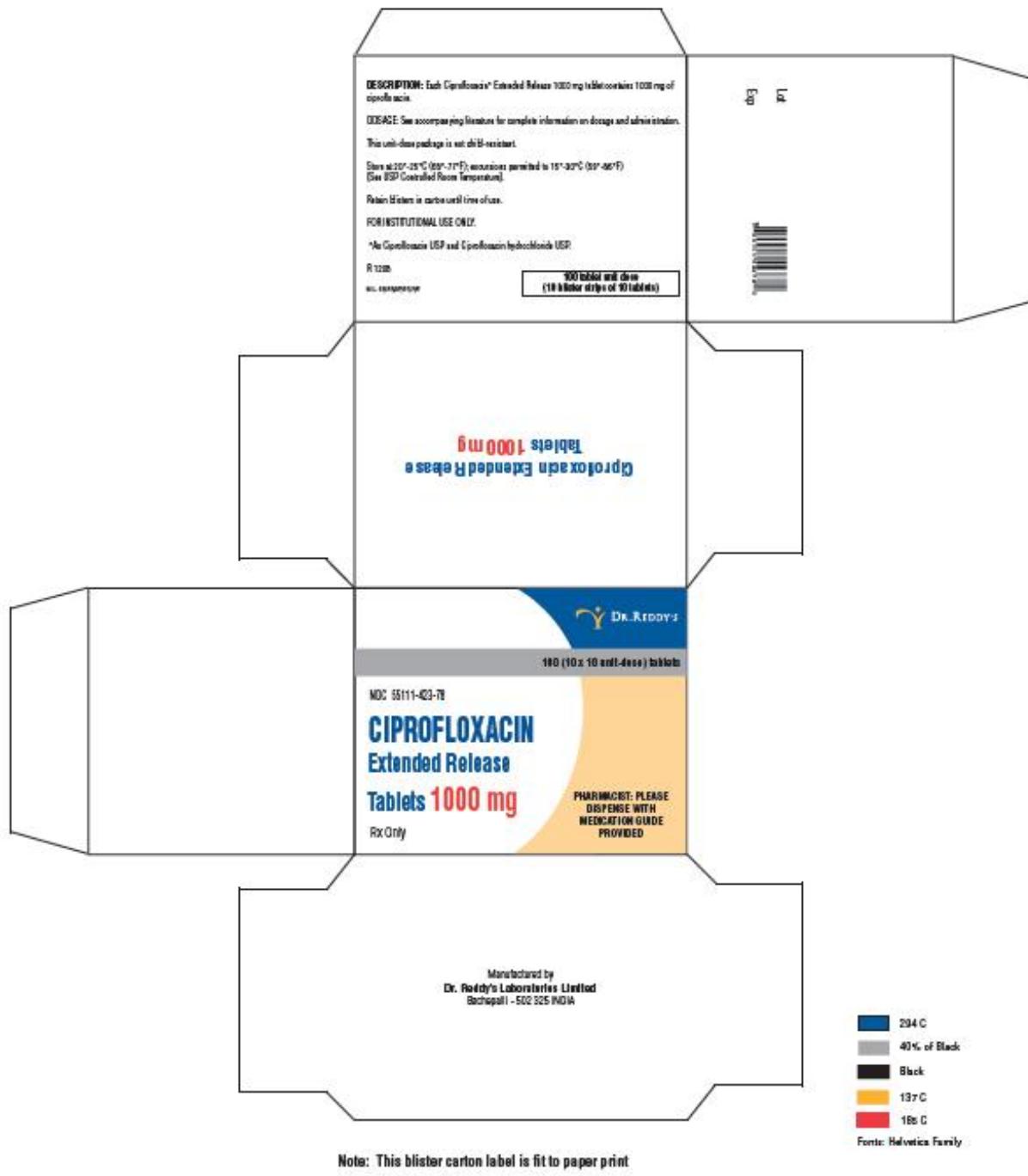
Mfg. By: Dr. Reddy's Laboratories Limited

Bachepalli - 502 325 INDIA



M.L.59RR/AP/97/F/R

LOT EXP



■ 294 C  
■ 40% of Black  
■ Black  
■ 137 C  
■ 18c C

Font: Helvetica Family

## CIPROFLOXACIN

ciprofloxacin hydrochloride tablet, film coated, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55111-422
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

ciprofloxacin hydrochloride (UNII: 4BA73M5E37) (ciprofloxacin - UNII:5E8K9I0O4U)	ciprofloxacin	287.5 mg
ciprofloxacin (UNII: 5E8K9I0O4U) (ciprofloxacin - UNII:5E8K9I0O4U)	ciprofloxacin	212.6 mg

## Inactive Ingredients

Ingredient Name	Strength
crosppovidone (UNII: 68401960MK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
ethylcelluloses (UNII: 7Z8S9VYZ4B)	
hypromelloses (UNII: 3NXW29V3WO)	
magnesium stearate (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
succinic acid (UNII: AB6MNQ6J6L)	
titanium dioxide (UNII: 15FIX9V2JP)	

## Product Characteristics

Color	WHITE (white to off-white )	Score	no score
Shape	OVAL (oblong shaped )	Size	19 mm
Flavor		Imprint Code	RDY;422
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55111-422-30	30 in 1 BOTTLE		
2	NDC:55111-422-01	100 in 1 BOTTLE		
3	NDC:55111-422-05	500 in 1 BOTTLE		
4	NDC:55111-422-78	100 in 1 BOX, UNIT-DOSE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077902	03/26/2007	

## CIPROFLOXACIN

ciprofloxacin hydrochloride tablet, film coated, extended release

## Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55111-423
Route of Administration	ORAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ciprofloxacin hydrochloride (UNII: 4BA73M5E37) (ciprofloxacin - UNII:5E8K9I0O4U)	ciprofloxacin	574.9 mg

ciprofloxacin (UNII: 5E8K9I0O4U) (ciprofloxacin - UNII:5E8K9I0O4U)	ciprofloxacin	425.2 mg
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## Inactive Ingredients

Ingredient Name	Strength
<b>crospovidone</b> (UNII: 68401960MK)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>ethylcelluloses</b> (UNII: 7Z8S9VYZ4B)	
<b>hypromelloses</b> (UNII: 3NXW29V3WO)	
<b>magnesium stearate</b> (UNII: 70097M6I30)	
<b>POLYETHYLENE GLYCOL 400</b> (UNII: B697894SGQ)	
<b>succinic acid</b> (UNII: AB6MNQ6J6L)	
<b>titanium dioxide</b> (UNII: 15FIX9V2JP)	

## Product Characteristics

<b>Color</b>	WHITE (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	OVAL (oblong shaped)	<b>Size</b>	23mm
<b>Flavor</b>		<b>Imprint Code</b>	RDY;423
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55111-423-30	30 in 1 BOTTLE		
2	NDC:55111-423-01	100 in 1 BOTTLE		
3	NDC:55111-423-05	500 in 1 BOTTLE		
4	NDC:55111-423-78	100 in 1 BOX, UNIT-DOSE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077701	10/31/2007	

**Labeler** - Dr. Reddy's Laboratories Limited (650562841)

## Establishment

Name	Address	ID/FEI	Business Operations
Dr.Reddy's Laboratories Limited		918608162	analysis, manufacture

Revised: 8/2011

Dr. Reddy's Laboratories Limited