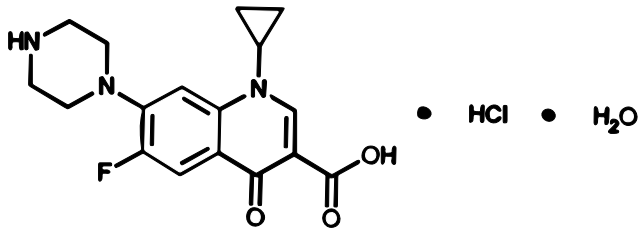
Proquin® XR
(ciprofloxacin hydrochloride)
Extended-Release Tablets, 500 mg

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Proquin XR and other antibacterial drugs, Proquin XR should be used only to treat uncomplicated urinary tract infections that are strongly suspected to be caused by bacteria.

DESCRIPTION

Proquin XR (ciprofloxacin hydrochloride) extended-release tablets contain ciprofloxacin hydrochloride, a synthetic broad-spectrum fluoroquinolone antimicrobial agent for oral administration.

Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride. The molecular weight of the monohydrate is 385.82. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



Proquin XR is available as 500 mg (ciprofloxacin equivalent) tablets. Proquin XR tablets are blue film-coated and oval-shaped. The inactive ingredients are povidone, magnesium stearate, polyethylene oxide, and film coating (Opadry® Blue).

CLINICAL PHARMACOLOGY

Absorption

When Proquin XR is administered with food, approximately 87% of ciprofloxacin is gradually released from the tablet over a 6-hour period. When administered following a meal maximum plasma ciprofloxacin concentrations are attained approximately 4.5-7 hours after dosing with Proquin XR tablets. Proquin XR should be administered with a main meal of the day, preferably the evening meal; if Proquin XR is given while fasting, the bioavailability will be lowered substantially. Administration of Proquin XR with a standardized meal (1000 calories, 50% fat) increased the C_{max} and AUC_{0-24h} by approximately 120% and 170%, respectively, compared to administration under fasting conditions; the mean T_{max} was prolonged from 2.3 hours to 4.5 hours. The following

table presents the pharmacokinetic parameters obtained at steady state for Proquin XR 500 mg qd versus CIPRO 250 mg bid.

Steady-State Pharmacokinetics for Ciprofloxacin in Plasma of Healthy Subjects (Day 3)[a]

Pharmacokinetic Parameters	***Proquin XR 500 mg Tablets (qd) (n=27)***	***CIPRO 250 mg Tablets (bid) (n=27)***
	Mean (%CV)	
$AUC_{0\text{-}24h}$ (mcg·hr/mL)	7.67 (25)	7.83 (16)
C_{max} (mcg/mL)	0.82 (28)	$C_{max,1}$ 0.57 (25)[b] $C_{max,2}$ 0.93 (27)
C_{min} (mcg/mL)	0.06 (42)	0.14 (29)
	Mean ± SD	
T_{max} (hr)	6.1 ± 2.6	T_{max1} 2.5 ± 1.2 [c] T_{max2} 2.5 ± 1.4

[a] both treatments were administered following a standardized meal (approximately 1000 calories, 50% fat).

[b] C_{max1} = peak concentration after the evening dose of CIPRO bid.
C_{max2} = peak concentration after the morning dose of CIPRO bid.

[c] T_{max1} = time of peak concentration after the evening dose CIPRO bid.
T_{max2} = time of peak concentration after the morning dose CIPRO bid.

Distribution

The *in vitro* binding of ciprofloxacin to plasma proteins over a concentration ranging from 0.9 to 30 micromolar is 9.9% to 36.6%, which is not likely to cause clinically significant protein binding interactions with other drugs.

Metabolism

Four metabolites of ciprofloxacin have been identified in human urine and feces. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The metabolites are desethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and formylciprofloxacin (M4), which account for approximately 11% of the total dose.

Elimination

The plasma elimination half-life of ciprofloxacin in healthy volunteers following a Proquin XR 500 mg dose was approximately 4.5 hours. Following a 500 mg oral dose of Proquin XR, 26.9% was excreted in the urine over 24 hours as unchanged drug for both formulations.

Following administration of a single 500 mg dose of Proquin XR, approximately 41% of the oral dose was excreted into the urine over 96 hours as unchanged drug and metabolites. The urinary excretion of ciprofloxacin was virtually complete within 24 hours after dosing. Urinary excretion is a main route of elimination of ciprofloxacin and its urinary concentrations relative to the MICs of the bacterial species may be important to understanding the efficacy of ciprofloxacin for the treatment of urinary tract

infections. The mean urinary ciprofloxacin concentration after dosing with Proquin XR 500 mg qd and CIPRO 250 mg bid are shown in the following table:

Mean Urinary Concentrations of Ciprofloxacin

Treatment	**Day**	**Mean (%CV) urinary ciprofloxacin concentration over 24 hours (mcg/mL)**
Proquin XR 500 mg once daily	1	71 (41)
	3	67 (28)
CIPRO 250 mg twice daily	1	79 (32)
	3	75 (24)

The renal clearance of ciprofloxacin following administration of Proquin XR, which is approximately 304 - 383 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.

Approximately 43% of the oral dose of Proquin XR is recovered from the feces as unchanged drug and metabolites within 7 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Drug Interactions

Antacids: The interaction of Proquin XR (administered as a single 1000 mg [2 x 500 mg] dose) and magnesium/aluminum-containing antacids (900 mg aluminum hydroxide and 600 mg magnesium hydroxide administered as a single oral dose) was evaluated in healthy volunteers. When Proquin XR was given 2 hours after antacids and 6 hours before antacids, the C_{max} values were similar to those when Proquin XR was given alone and AUC values were reduced by approximately 10%. When Proquin XR was given 4 hours before antacids, C_{max} was reduced by approximately 11% and AUC was reduced by approximately 22%. Thus, to minimize the effect of antacids on the absorption of ciprofloxacin, Proquin XR should be given either 2 hours after or at least 4 hours before antacids (see **PRECAUTIONS, Drug Interactions,** and **Information for Patients**).

Caffeine: Some quinolones, including ciprofloxacin also decrease caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See **PRECAUTIONS: Drug Interactions**)

Calcium-containing beverages: Concomitant administration of ciprofloxacin with milk products or calcium-fortified juices alone should be avoided since decreased absorption is possible. (See **PRECAUTIONS: Drug Interactions** and **Information for Patients**, and **DOSAGE AND ADMINISTRATION**)

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

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

Multivalent cation-containing products: Concomitant administration of ciprofloxacin with sucralfate, VIDEX® (didanosine) chewable/buffered tablets, metal cations such as iron and calcium, and multivitamin preparations with zinc should be avoided. (See **PRECAUTIONS: Drug Interactions** and **Information for Patients**)

Omeprazole: When Proquin XR was administered following a meal as a single 1000 mg dose (2 x 500 mg), 2 hours after the third dose of omeprazole (given 40 mg once daily for three days) to 27 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were bioequivalent to the mean AUC and C_{max} values when Proquin XR was administered alone. Omeprazole should be taken as directed and Proquin XR should be taken with a main meal of the day, preferably the evening meal. (See **PRECAUTIONS: Drug Interactions and Information for Patients**).

Probenecid: Co-administration of probenecid with fluoroquinolones results in a reduction in the renal clearance and an increase in their concentrations in the systemic circulation.

Theophylline: Previous studies with quinolones, including ciprofloxacin, have shown that concomitant administration of these drugs with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing central nervous system (CNS) or other adverse reactions. (See **WARNINGS, PRECAUTIONS: Drug Interactions**)

Warfarin: Ciprofloxacin and other quinolones have been reported to enhance the effects of the oral anticoagulant, warfarin, or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The co-administration of single doses of Proquin XR and Coumadin® (7.5 mg) did not result in significant changes in the pharmacokinetics of ciprofloxacin nor did it significantly affect the pharmacodynamics of S-warfarin and R-warfarin. Although the C_{max} and AUC of the two warfarin enantiomers and the elimination half-life of S-warfarin were not significantly altered by ciprofloxacin co-administration, the half-life of R-warfarin was statistically significantly prolonged (P=0.029). (See **PRECAUTIONS: Drug Interactions**)

Special Populations

Elderly: When a single 500 mg dose of Proquin XR was administered to elderly subjects (>65 years) C_{max} and AUC values were increased by approximately 24% and 20% respectively, compared to younger subjects from a reference study. This can be at least partially attributed to decreased renal clearance in the elderly. However, in elderly subjects, the percentage of the ciprofloxacin dose excreted in the urine was 11% lower as compared to younger subjects. The elimination half-life was not significantly prolonged in elderly subjects (4.9 hours) compared to healthy young subjects (4.5 hours). These differences are not considered clinically significant. (See **PRECAUTIONS: Geriatric Use**)

Renal Impairment: After receiving a single dose of Proquin XR 500 mg, the ciprofloxacin $AUC_{0\text{-}24h}$ in subjects with mild renal impairment (CLcr = 51-80 mL/min;

n=10) and moderate renal impairment (CLcr = 30-50 mL/min; n=10) were 42% and 54% greater, respectively, compared to subjects with normal renal function (CLcr >80 mL/min; n=10). The elimination half-life of ciprofloxacin in patients with mild and moderate renal impairment was approximately 1.7 times longer as compared to the control group (7.8 – 7.5 hours versus 4.5 hours). In patients with end-stage renal disease (CLcr <10 mL/min), the half-life of ciprofloxacin is approximately doubled compared to subjects with normal renal function. No dose adjustment of Proquin XR is required for patients with uUTI and mild to moderate renal impairment. The efficacy of Proquin XR has not been studied in patients with severe renal impairment. (See **DOSAGE AND ADMINISTRATION**)

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

Pediatrics: The pharmacokinetics of Proquin XR have not been studied in pediatric populations.

MICROBIOLOGY

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

Ciprofloxacin is 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 MIC by more than a factor of 2.

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

Aerobic gram-negative microorganisms

Escherichia coli
Klebsiella pneumoniae

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

Ciprofloxacin exhibits *in vitro* MICs of 1 mcg/mL or less against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of Proquin XR in

treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms

Proteus mirabilis

Susceptibility Tests

Interpretive criteria for urinary isolates have not been established for Proquin XR. Interpretive criteria established based on systemic drug levels may not be appropriate for uncomplicated urinary tract infections.

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

For testing *Enterobacteriaceae*:

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration 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 concentration usually achievable; other therapy should be selected.

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

Microorganism		MIC Range (mcg/mL)
Escherichia coli	ATCC 25922	0.004-0.015
Staphylococcus aureus	ATCC 29213	0.12-0.5

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to

antimicrobial compounds. One such standardized procedure [2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-mcg 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-mcg ciprofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

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

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

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

Microorganism		**Zone Diameter (mm)**
Escherichia coli	ATCC 25922	30-40
Staphylococcus aureus	ATCC 25923	22-30

INDICATIONS AND USAGE

Proquin XR is indicated only for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms listed below. Proquin XR is not interchangeable with other ciprofloxacin extended-release or immediate release oral formulations. See **DOSAGE AND ADMINISTRATION** for specific recommendations.

Uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli* and *Klebsiella pneumoniae.*

THE SAFETY AND EFFICACY OF PROQUIN XR IN TREATING PYELONEPHRITIS, COMPLICATED URINARY TRACT INFECTIONS, AND INFECTIONS OTHER THAN UNCOMPLICATED URINARY TRACT INFECTIONS HAVE NOT BEEN DEMONSTRATED. Alternative therapy should be considered for patients who remain symptomatic or develop fever and back pain while on treatment with Proquin XR.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Proquin XR and other antibacterial drugs, Proquin XR should only be used to treat

uncomplicated urinary tract infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and sensitivity information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

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

WARNINGS

THE SAFETY AND EFFECTIVENESS OF PROQUIN XR IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. **(**See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.**)**

Ciprofloxacin, as with other members of the quinolone class, causes arthropathy and/or chondroplasia in immature dogs. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. The relevance of these findings to the clinical use of ciprofloxacin is unknown. (See **ANIMAL PHARMACOLOGY**)

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

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

Hypersensitivity Reactions: 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
- inertstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and apalstic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hemtologic 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 Proquin XR, 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 muse be considered in all patients who represent with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dyesthesias, 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.

Tendon Effects: Ruptures of the shoulder, hands, Achilles or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially elderly patients. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon ruptures can occur during or after therapy with quinolones, including ciprofloxacin.

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 CNS events, including nervousness, agitation, insomnia, anxiety, nightmares, or paranoia. (See **WARNINGS**)

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

Prescribing Proquin XR in the absence of a strongly suspected bacterial infection is unlikely to benefit the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Patients should be advised:

- that antibacterial drugs, including Proquin XR, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Proquin XR is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Proquin XR or other antibacterial drugs in the future.

- that Proquin XR should only be used to treat uncomplicated urinary tract infections (also known as bladder infections). The safety and efficacy of Proquin XR to treat other urinary tract or non-urinary tract infections have not been studied.

- that Proquin XR should be taken with a main meal of the day, preferably the evening meal. The patient should not take more than one Proquin XR tablet per day, even if the patient misses a dose.

- that Proquin XR tablets should be taken whole and never split, crushed, or chewed.

- that concomitant administration of Proquin XR with aluminum or magnesium-containing antacids, sucralfate, VIDEX® (didanosine) chewable buffered tablets or pediatric powder, metal cations such as iron and calcium, and multivitamin preparations containing zinc should be avoided. Proquin XR should be administered at least 4 hours before or 2 hours after these products. (See **CLINICAL PHARMACOLOGY: Drug Interactions, DOSAGE AND ADMINISTRATION**, and **PRECAUTIONS: Drug Interactions**)

- that Proquin XR should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, since the absorption of ciprofloxacin may be significantly reduced. However, Proquin XR may be taken with a meal that contains these products. (See **CLINICAL PHARMACOLOGY: Drug Interactions** and **PRECAUTIONS: Drug Interactions**)

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

- to avoid excessive sunlight or artificial ultraviolet (UV) light while receiving Proquin XR and to discontinue therapy if phototoxicity occurs.

- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, patients should discontinue treatment and contact their physician.

- to discontinue Proquin XR treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon. The risk of serious tendon disorders with quinolones is higher in those over 65 years of age, especially those of corticosteroids.

- to contact their doctor if they do not feel better or if they develop fever and back pain while or after taking Proquin XR.

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

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

- that convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking this drug 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

Caffeine: 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.

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

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

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

Methotrexate: 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 toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Multivalent cation-containing products: Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium or aluminum antacids, sucralfate, VIDEX® chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. Proquin XR should be administered at least 4 hours before or 2 hours after these products. This time window is different than for other oral formulations of ciprofloxacin, which are usually administered 2 hours before or 6 hours after antacids. (See **CLINICAL PHARMACOLOGY: Drug Interactions, PRECAUTIONS: Information for Patients,** and **DOSAGE AND ADMINISTRATION**)

Non-steroidal anti-inflammatory drugs (but not aspirin): These drugs in combination with very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

Omeprazole: The rate and extent of absorption of ciprofloxacin was bioequivalent when Proquin XR was given alone or when Proquin XR was given 2 hours after omeprazole at the dose that maximally suppresses gastric acid secretion. Omeprazole should be taken as directed and Proquin XR should be taken with a main meal of the day, preferably the evening meal. (See **CLINICAL PHARMACOLOGY: Drug Interactions** and **Information for Patients**).

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

Probenecid: Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in serum.

Theophylline: 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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rodent carcinogenicity studies were not required. Two *in vitro* mutagenicity tests were conducted with ciprofloxacin:

- Bacterial Reverse Mutation Assay; negative for mutagenicity in the presence and absence of an S-9 metabolic activation system.
- Chinese Hamster Ovary (CHO) Chromosomal Aberration Assay; positive for inducing chromosomal aberrations.

In addition to the *in vitro* genotoxicity assays, an *in vivo* rat micronucleus study with ciprofloxacin was negative.

Fertility studies performed with male and female rats at oral doses of ciprofloxacin up to 600 mg/kg/day (approximately 10-fold the recommended 500 mg therapeutic dose based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C

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

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

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

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

Embryo/fetal developmental toxicity studies were conducted in pregnant rats and rabbits using oral doses up to 600 mg/kg/day in rats and 30 mg/kg/day in rabbits. Fetal development (skeletal variation) was affected in rats at the maternally toxic dose of 600 mg/kg/day (approximately 1.8-fold the recommended 500 mg therapeutic dose based upon plasma AUC measure of systemic exposure). The maternally toxic 30 mg/kg/day dose to pregnant rabbits resulted in abortions and body weight gain depression; embryo/fetal lethality and skeletal developmental effects were observed at this dose level (approximately 1.2-fold the recommended therapeutic dose based upon body surface area). The 10 mg/kg/day dose level, although maternally toxic, did not induce embryo/fetal developmental effects. A peri/postnatal developmental toxicity study with pregnant/lactating female rats exhibited no developmental effects to the F_1 pups at the highest dose level of 600 mg/kg/day; the 300 and 600 mg/kg/day dose levels were maternally toxic to the pregnant dams based upon slight body weight gain reduction. No evidence of compound-related fetal malformation was observed in any of the reproductive toxicity studies.

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 ciprofloxacin taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Proquin XR in pediatric patients and adolescents less than 18 years of age have not been established. Quinolones, including ciprofloxacin, cause arthropathy in juvenile animals. (See **WARNINGS**)

Geriatric Use

Clinical experience with Proquin XR did not include sufficient number of subjects 65 years of age or older to determine whether they respond differently than younger subjects. Reported clinical experience with other formulations of ciprofloxacin has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is 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. (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 ProQuin XR with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for torsades de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

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

ADVERSE REACTIONS

Two clinical trials enrolled 1,095 patients, of whom 547 patients received Proquin XR 500 mg once daily and 538 patients received CIPRO 250 mg twice daily for 3 days. The patients were followed for approximately 5 weeks after the end of study drug dosing. Most adverse events reported were described as mild to moderate in severity and required no treatment. Proquin XR was discontinued due to adverse reactions thought to be drug-related in 0.5% of patients.

The incidence of all adverse events (regardless of relationship to study drug) reported for at least 2% of patients treated with Proquin XR during the entire 5-week study period was as follows: fungal infection (2.6%), nasopharyngitis (2.6%), headache (2.4%), and micturition urgency (2.0%).

The incidence of adverse events (regardless of relationship to study drug) reported for at least 1% of patients treated with Proquin XR during study drug treatment and up to 3 days after study drug was headache (1.5%).

The incidence of adverse events, judged by investigators to be at least possibly drug-related, occurring any time during the study in at least 1% of Proquin XR-treated patients was fungal infection (1.6%).

Additional uncommon events, judged by the investigator to be at least possibly drug-related, occurring at any time during the study in less than 1% of Proquin XR-treated patients were:

Cardiac Disorders: ventricular bigeminy.

Immune System Disorders: hypersensitivity.

Gastrointestinal Disorders: abdominal pain, nausea, diarrhea, dyspepsia, aggravated irritable bowel syndrome, lower abdominal pain, vomiting.

General Disorders: suprapubic pain, fatigue, pain, rigors, tenderness.

Infections and Infestations: urinary tract infection, fungal vaginosis, bacterial vaginitis, vaginal candidiasis, vaginal infection, vaginitis.

Investigations: blood bilirubin increased, alanine aminotransferase increased, abdominal aortic bruit, aspartate aminotransferase increased, body temperature increased.

Musculoskeletal and Connective Tissue Disorders: joint swelling, muscle spasms, night cramps.

Nervous System Disorders: headache, dizziness, disturbance in attention, paresthesia.

Renal and Urinary Disorders: micturition urgency, dysuria, urinary frequency, abnormal urine odor.

Reproductive System and Breast Disorders: female genital pruritus.

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea.

Skin/Subcutaneous Tissue Disorders: rash, pruritus, urticaria.

Reported Post-Marketing Adverse Events with Other Formulations of Ciprofloxacin

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

Abnormal gait, achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions), 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, depression, diplopia, drowsiness, dysphagia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, fixed eruptions, flushing, gastrointestinal bleeding, gout (flare up), grand mal convulsion, gynecomastia, hallucinations, hearing loss, hematuria, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic failure (including fatal cases), hepatic necrosis, hepatitis, hiccup, hyperesthesia, hyperpigmentation, hypertension, hypertonia, hypoesthesia, hypotension, ileus, insomnia, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lipase increase, lymphadenopathy, malaise, manic reaction, marrow depression, migraine, moniliasis (oral, gastrointestinal, vaginal), mouth dryness, myalgia, myasthenia, myasthenia gravis (possible exacerbation), myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, extremities, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, pancytopenia, paranoia, paresthesia, peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, 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, syncope, tachycardia, taste loss, tendonitis, tendon

rupture, tinnitus, torsade de pointes, toxic epidermal necrolysis, toxic psychosis, tremor, 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), weakness.

Reported Laboratory Changes with Proquin XR and Other Formulations of Ciprofloxacin

The following laboratory adverse events were reported for Proquin XR-treated patients during clinical trials: anemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, and hematuria. All events were reported for <1% of Proquin XR-treated patients, except for hematuria (1.2%).

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, eosinophils counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatinine 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, methemaglobinemia, pancytopenia.

OVERDOSAGE

In the event of an acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis. Serious adverse effects were not observed in rats receiving single oral doses of ciprofloxacin as high as 2,000 mg/kg.

DOSAGE AND ADMINISTRATION

Proquin XR and other oral formulations of ciprofloxacin are not interchangeable. Proquin XR should be administered orally once daily for 3 days with a main meal of the day, preferably the evening meal. Proquin XR should be administered at least 4 hours before or 2 hours after antacids containing magnesium or aluminum, sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations containing zinc.

Proquin XR tablets should be taken whole and never split, crushed, or chewed. (See **CLINICAL PHARMACOLOGY: Drug Interactions**)

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 patient with uUTI and mild to moderate renal impairment. The efficacy of Proquin XR has not been studied in patients with severe renal impairment. (See **CLINICAL PHARMACOLOGY: Special Populations** and **PRECAUTIONS: Geriatric Use**)

Impaired Liver Function:

No dosage adjustment is required with Proquin XR in patients with stable chronic cirrhosis. However, the pharmacokinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been fully elucidated. (See **CLINICAL PHARMACOLOGY**: **Special Populations**)

HOW SUPPLIED

Proquin XR is available as blue film-coated tablets containing 500 mg ciprofloxacin. The tablet is debossed with "500"on one side and "DMI" on the other side.

Package	Strength	NDC Code
Bottles of 30	500 mg	15456-001-30
Bottles of 50	500 mg	13913-001-50
Blister Packs of 3	500 mg	15456-001-03

Store Proquin XR at 25 °C (77 °F); excursion permitted to 15-30 °C (59-86 °F)

ANIMAL PHARMACOLOGY

There were no indications of gastrointestinal or other toxic effects due to oral administration of Proquin XR tablets to male and female beagle dogs at doses up to 1000 mg/day for 28 days (approximately 2.6- and 4.9-fold [male and female dogs, respectively] the recommended therapeutic dose based upon AUC measures of systemic exposure).

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**)

Crystalluria, *sometimes associated with secondary nephropathy,* occurs in laboratory animals dosed with the fluoroquinolone class of drugs. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals. In contrast, crystalluria is rare in man since human urine is typically acidic.

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

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals. There was no indication of ocular toxicity in the dog study cited above.

CLINICAL STUDIES

Proquin XR was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled trial conducted in the US. This study compared Proquin XR (500 mg once daily for 3 days) with ciprofloxacin immediate-release tablets (CIPRO® 250 mg twice daily for 3 days). Of the 1,037 patients enrolled, 524 were randomly assigned to the Proquin XR treatment group and 513 were randomly assigned to the control group. A total of 272 (52%) patients in the Proquin XR group and 251 (49%) in the CIPRO group were evaluable for efficacy and included in the Per-Protocol population. The primary efficacy variable was bacteriologic

eradication of the baseline organism(s) with no new infection at the Test-of-Cure (TOC) visit (Day 4 to 11 post-therapy).

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

Bacteriological Eradication and Clinical Cure Rates at the Test-of-Cure (TOC) Visit

	Proquin XR 500 mg qd x 3 Days	**CIPRO 250 mg bid x 3 Days**
Randomized Patients	524	513
Per Protocol Patients	272 (52%)	251 (49%)
Bacteriologic Eradication with no new infection at TOC	212 / 272 (78%)	193 / 251 (77%)
	(-6.2%, 8.2%)	
Clinical Response at TOC	233 / 272 (86%)	216 / 251 (86%)
	(-6.4%, 5.6%)	
Bacteriologic Eradication by organism*		
E. coli	211 / 222 (95%)	184 / 202 (91%)
K. pneumoniae	11 / 12 (92%)	10 / 13 (77%)

*Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism.

The bacteriological eradication rates for baseline organisms at the TOC visit were 93% (254/272) for Proquin XR and 90% (225/251) for CIPRO. Of the patients with their baseline organism eradicated, new infections were detected in 42/254 (16.5%) Proquin XR-treated patients and 32/225 (14.2%) CIPRO-treated patients at the TOC visit. Gram-negative rods were responsible for new infections in 10 Proquin XR-treated patients and 7 CIPRO-treated patients, and *Enterococcus* species were isolated in 24 Proquin XR-treated patients, and 20 CIPRO-treated patients.

REFERENCES

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

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

PATIENT INFORMATION ABOUT PROQUIN XR

PROQUIN® XR

(prōkwin)

(ciprofloxacin hydrochloride)

Extended-Release Tablets, 500 mg

This leaflet contains important information about Proquin XR (ciprofloxacin hydrochloride) extended-release tablets and should be read before you begin treatment. This leaflet does not replace talking with your doctor about your medical condition or your treatment. This leaflet does not list all benefits and risks of Proquin XR. Proquin XR can be prescribed only by a doctor. If you have any questions about Proquin XR, talk to your doctor. Only your doctor can tell you if Proquin XR is right for you.

What is Proquin XR?

Proquin XR is an antibiotic in the class known as "quinolones" that is used to treat adults with simple (uncomplicated) urinary tract infections (also known as "bladder infections") caused by bacteria. It is not known if Proquin XR will treat infections other than bladder infections. Proquin XR, like all other antibiotics, does not kill viruses.

You should contact your doctor if you do not feel better or if you develop fever and back pain while or after taking Proquin XR.

Proquin XR tablets are blue and contain 500 mg of active drug.

How should I take Proquin XR?

- Proquin XR should be taken once a day for 3 days shortly after a main meal of the day, preferably the evening meal. Proquin XR does not work as well if you take it without a meal. You should try to take Proquin XR at about the same time each day.

- Take Proquin XR for all 3 days, even if you are feeling better. If you stop taking Proquin XR before all 3 doses, Proquin XR may not cure your bladder infection.

- **Do not split, crush, or chew Proquin XR tablets.** Proquin XR tablets must be swallowed whole. Tell your doctor if you cannot swallow tablets whole. Your doctor will prescribe a different medicine for you.

- Do not take more than one Proquin XR tablet a day, even if you miss a dose.

- Do not take Proquin XR at the same time that you drink milk or juices with added calcium, unless you drink them with a main meal.

- Many antacids and multivitamins may interfere with the absorption of Proquin XR if taken at the same time. Take Proquin XR at least 4 hours before or 2 hours after antacids that contain magnesium or aluminum. Proquin XR should also be taken at least 4 hours before or 2 hours after sucralfate, VIDEX® (didanosine) chewable buffered tablets or pediatric powder, iron, calcium, and vitamins that contain zinc.

Who should not take Proquin XR?

Do not take Proquin XR if you are allergic to or have ever had a severe reaction to ciprofloxacin or to any other "quinolone" antibiotics.

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

Proquin XR is not recommended for children.

What should I tell my doctor before taking Proquin XR?

Tell you doctor about all of your medical conditions, including if you have or ever had seizures (epilepsy), asthma, or liver or kidney problems.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. Proquin XR and certain other medicines can affect each other. You may have to adjust the times you take certain other medicines, vitamins, and herbal supplements. Especially, tell your doctor if you take: theophylline, VIDEX® (didanosine) chewable buffered tablets or pediatric powder; warfarin (Coumadin®); glyburide (Glucovance®, Micronase®, DiaBeta®); phenytoin (Dilantin®); sucralfate (Carafate®); or antacids or vitamins that contain magnesium, calcium, aluminum, iron, or zinc.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

What are the possible side effects of Proquin XR?

Proquin XR is generally well tolerated. The most common side effects with Proquin XR include vaginal yeast infection and headache. Less common side effects include nausea, diarrhea, dizziness, and abdominal pain.

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

Rare cases of allergic reactions have been reported in patients receiving quinolones, including ciprofloxacin, even after just one dose. Stop taking Proquin XR and call your doctor or get emergency medical attention right away if you develop a rash, hives, swelling of your face or throat, or have trouble breathing.

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

Pain, swelling, and tears of Achilles, shoulder, or hand tendons have been reported in patients receiving fluoroquinolones, including Proquin XR. The risk for tendon effects is higher if you are over 65 years of age, and especially if you are taking corticosteroids. If you develop pain, swelling, or rupture of a tendon you should stop taking ciprofloxacin, refrain from exercise and strenuous use of the affected area, and contact your health care provider.

Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. Tell your doctor if you have experienced convulsions in the past. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression. Stop taking Proquin XR and call your doctor right away if you get any of these symptoms.

Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antibiotics including with Proquin XR. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your physician as soon as possible.

These are not all the side effects with Proquin XR. For more information, ask your doctor or pharmacist.

How should I store Proquin XR?

- Store Proquin XR at room temperature, 59° to 86°F (15° to 30°C).
- Keep Proquin XR and all medicines out of the reach of children.

What are the ingredients in Proquin XR?

Active Ingredient: ciprofloxacin hydrochloride

Inactive Ingredients: film coating, magnesium stearate, polyethylene oxide, and povidone.

General information about Proquin XR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Proquin XR for a condition for which it was not prescribed. Do not give Proquin XR to other people, even if they have the same symptoms you have. It may harm them.

Keep this medication out of the reach of children.

This leaflet summarizes the most important information about Proquin XR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Proquin XR that is written for health care professionals. Further information is also provided at:

Medical Inquiries: 1-866-230-0375 and www.proquinxr.com

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East Brunswick, NJ 08816

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