HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Proquin XR safely and effectively. See full prescribing information for Proquin XR.

Proquin® XR (ciprofloxacin) Extended-Release Tablets, 500 mg*
***present as 582 mg of ciprofloxacin hydrochloride monohydrate**

Initial U.S. Approval: 1987

WARNING: TENDINITIS/TENDON RUPTURE

See full prescribing information for complete boxed warning.

Fluoroquinolones, including Proquin XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk further increased in patients over 60 years of age, taking corticosteroid drugs, and in patients with kidney, heart and lung transplant recipients (5.1).
Fluroquinolones, including Proquin XR, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Proquin XR in patients with known history of myasthenia gravis (See Warnings).

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

INDICATIONS AND USAGE

Proquin XR is a fluoroquinolone antibacterial indicated for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms (1.1).

Not interchangeable with other ciprofloxacin extended-release or immediate release oral formulations (1.2).

Safety and efficacy in treating pyelonephritis, complicated urinary tract infections, and infections other than uncomplicated urinary tract infections have not been demonstrated (1.2).

DOSAGE AND ADMINISTRATION

- Take orally once daily for 3 days with a main meal of the day, preferably the evening meal (2)
- Take whole. Never split, crush, or chew tablets (2)

DOSAGE FORMS AND STRENGTHS

Extended release tablets: 500 mg* of ciprofloxacin (3)
*present as 582 mg of ciprofloxacin hydrochloride monohydrate

CONTRAINDICATIONS

Known hypersensitivity to ciprofloxacin or other quinolones (4, 5.2).

WARNINGS AND PRECAUTIONS

- Risk of tendinitis and tendon rupture is increased. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs (5.1, 8.5)
- Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. Discontinue drug use at first sign of skin rash, jaundice or any other sign of hypersensitivity. (5.2, 5.3)
- CNS effects: Dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts can occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold (5.5)
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs (5.6)
- Peripheral neuropathy: Discontinue if symptoms occur (5.7)

ADVERSE REACTIONS

The most common adverse reactions (≥ 2%) were fungal infection, nasopharyngitis, headache, and micturition urgency (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Depomed, Inc. at 1-866-458-6389 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Theophylline: Serious and fatal reactions; avoid concurrent use or monitor serum concentrations (5.4, 7.1)
- Multivalent cation-containing products, including antacids, metal cations or didanosine: Decreased absorption of Proquin XR; take at least 2 hours before or 4 hours after Proquin XR (2, 7.2)
- Milk and other calcium-containing beverages: Decreased Proquin XR absorption; avoid. concomitant use (2, 7.3)
- Warfarin: Anticoagulant effect can be enhanced; monitor prothrombin time, INR; watch for bleeding (7.4)
- Cyclosporine: Increased serum creatinine; monitor cyclosporine whole blood concentrations (7.5)
- Methotrexate: Can increase methothrexate concentrations; monitor for methotrexate toxic reactions (7.6)
- Phenytoin: Increased or decreased phenytoin concentrations; monitor phenytoin concentrations (7.7)
- Glyburide: Risk of dysglycemia; monitor blood glucose (7.8)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. Use only if the potential benefit justifies the risk (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)
- Geriatric: Increased risk for severe tendon disorders further increased by concomitant corticosteroid therapy; also increased risk of prolongation of the QT interval (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 02/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: TENDONITIS AND TENDON RUPTURE

Fluoroquinolones, including Proquin XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart and lung transplant recipients [*See Warnings and Precautions (5.1, 8.5)*].
Fluroquinolones, including Proquin XR, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Proquin XR in patients with known history of myasthenia gravis (See Warnings).

1 INDICATIONS AND USAGE

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. 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.

1.1 Uncomplicated Urinary Tract Infections

Proquin XR is indicated for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *Escherichia coli* and *Klebsiella pneumoniae*.

1.2 Limitations of Use

Proquin XR is not interchangeable with other ciprofloxacin extended-release or immediate release oral formulations.

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.

2 DOSAGE AND ADMINISTRATION

Proquin XR 500 mg tablets should be administered orally once daily for 3 days with a main meal of the day, preferably the evening meal.

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

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 [see *Drug Interactions (7.2)*].

Concomitant administration of ciprofloxacin with milk products or calcium-fortified juices alone should be avoided since decreased absorption is possible [see *Drug Interactions (7.3)*].

Adequate hydration of patients receiving Proquin XR should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria has been reported with quinolones [see *Adverse Reactions (6.1)* and *Patient Counseling Information (16.2)*].

3 DOSAGE FORMS AND STRENGTHS

Extended release tablets: 500 mg* of ciprofloxacin

***present as 582 mg of ciprofloxacin hydrochloride monohydrate**

4 CONTRAINDICATIONS

Proquin XR is contraindicated in persons with a known hypersensitivity to ciprofloxacin or other quinolone antibacterials [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including Proquin XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Proquin XR should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug [see *Adverse Reactions (6.3)*].

5.2 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including Proquin XR, 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 **Proquin XR** in patients with known history of myasthenia gravis. **[See PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Reported Post-Marketing Adverse Events with Other Formulations of Ciprofloxacin).**

5.3 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including ciprofloxacin. These reactions

often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Proquin XR should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated [see *Adverse Reactions (6.3)*].

5.4 Other Serious and Sometimes Fatal 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 *Adverse Reactions (6.3)*].

5.5 Theophylline

Serious and fatal reactions have been reported in patients receiving theophylline concurrently with fluoroquinolones, including ciprofloxacin. 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 concentrations of theophylline should be monitored and dosage adjustments made as appropriate [see *Drug Interactions (7.1)*].

5.6 Central Nervous System Effects

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 *Adverse Reactions (6), Drug Interactions (7)*].

5.7 *Clostridium difficile*-Associated Diarrhea

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 must 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 [see *Adverse Reactions (6)*].

5.8 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 [see *Adverse Reactions (6)*].

5.9 Arthropathic Effects in Animals

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 *Use in Specific Populations (8.4), Nonclinical Toxicology (13.2)*].

5.10 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 (6.3)*].

5.11 Development of Drug Resistant Bacteria

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

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Tendon Effects [see *Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.2)*]
- Other Serious and Sometimes Fatal Reactions [see *Warnings and Precautions (5.3)*]
- Central Nervous System Effects [see *Warnings and Precautions (5.5)*]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions (5.6)*]
- Peripheral Neuropathy [see *Warnings and Precautions (5.7)*]
- Photosensitivity/Phototoxicity [see *Warnings and Precautions (5.9)*]
- Development of Drug Resistant Bacteria [see *Warnings and Precautions (5.10)*]

Crystalluria and cylindruria have been reported with quinolones, including ciprofloxacin. Therefore, adequate hydration of patients receiving Proquin XR should be maintained to prevent the formation of highly concentrated urine [see *Dosage and Administration (2)*].

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Proquin XR in 524 patients in one clinical trial. The population studied had a mean age of 39 years (approximately 93.4% of the population were < 65 years of age), 100% were female, 77% were Caucasian and 7.4% were Black. Patients received Proquin XR 500 mg once daily for 3 days. Patients were followed for approximately 5 weeks after the end of study drug dosing.

Discontinuation of Proquin XR occurred in 1.4% of patients. Each of the discontinuations were for a different adverse reactions. Refer to Table 1.

The most common adverse reactions (≥ 2%) were fungal infection, nasopharyngitis, headache, and micturition urgency.

Table 1: Adverse reactions (regardless of relationship to study drug) occurring in ≥1% of Proquin XR-treated patients (500 mg once daily for 3 days) during the entire study period compared to ciprofloxacin-immediate release tablets (250 mg twice daily for 3 days)

Adverse Reaction	Proquin XR	Ciprofloxacin-immediate release tablets
Nausea	1.4	2.4
Abdominal pain	1.7	1.2
Suprapubic pain	1.4	0.6
Urinary tract infection	10.8	9.8
Fungal infection	2.7	1.8

Adverse Reaction	Proquin XR	Ciprofloxacin-immediate release tablets
Upper respiratory tract infection	1.4	2.9
Back pain	1.7	1.6
Headache	2.3	3.9
Micturition urgency	1.9	1.0
Urinary frequency	1.4	1.0
Nasopharyngitis	2.7	1.4
Pharyngitis	1.2	1.0

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%).

Less common reactions, 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, hematuria.
- **Reproductive System and Breast Disorders:** female genital pruritus.
- **Respiratory, Thoracic, and Mediastinal Disorders:** dyspnea.
- **Skin/Subcutaneous Tissue Disorders:** rash, photosensitivity/ phototoxicity reaction, pruritus, urticaria.

6.3 Adverse Reactions Reported with Other Systemic Formulations of Ciprofloxacin

In addition, to the adverse reactions reported with Proquin XR, the following adverse reactions have been reported during clinical trials and from worldwide post-marketing experience with other systemic formulations of ciprofloxacin (includes all dosages and 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.

Abnormal gait, achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions) [see *Contraindications (4)* and *Warnings and Precautions (5.2)*], 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 [see *Warnings and Precautions (5.5)*], 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) [see *Warnings and Precautions (5.3)*], 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 [see *Warnings and Precautions (5.7)*], peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, photosensitivity/phototoxicity reaction[see *Warnings and Precautions (5.9)*] pleural effusion, polyuria, postural hypotension, prothrombin time prolongation, pseudomembranous colitis (the onset of symptoms may occur during or after antimicrobial treatment) [see *Warnings and Precautions (5.6)*], 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 [see *Boxed Warning* and *Warnings and Precautions (5.1)*], 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.

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.

7 DRUG INTERACTIONS

7.1 Theophylline

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline, which may result in an increased risk of a patient developing central nervous system (CNS) or other adverse reactions. If concomitant use cannot be avoided, serum concentrations of theophylline should be monitored and dosage adjustments made as appropriate [see *Warnings and Precautions (5.4)*].

7.2 Antacids and Other Products Containing Multivalent Cations

Concurrent administration of quinolones, 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. Proquin XR should be given either 2 hours after or at least 4 hours before 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 *Dosage and Administration (2) and Clinical Pharmacology (12.3)*].

7.3 Calcium-containing Beverages

Concomitant administration of ciprofloxacin with milk products or calcium-fortified juices alone should be avoided since decreased absorption of Proquin XR is possible [see *Dosage and Administration (2)*].

7.4 Warfarin

Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be monitored if Proquin XR is administered concomitantly with warfarin or other oral anticoagulants. Patients should also be monitored for evidence of bleeding [see *Adverse Reactions (6.3) and Clinical Pharmacology (12.3)*].

7.5 Cyclosporine

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly. Cyclosporine whole blood trough concentrations should be monitored when given concomitantly with Proquin XR.

7.6 Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma concentrations 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.

7.7 Phenytoin

Altered serum concentrations of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin. Phenytoin serum concentrations should be monitored when given concomitantly with Proquin XR.

7.8 Glyburide

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

7.9 Non-steroidal Anti-inflammatory Drugs (NSAIDs), but not Aspirin

NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in nonclinical studies [see *Nonclinical Toxicology (13.2)*.

7.10 Caffeine

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

7.11 Probenecid

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces increased concentrations of ciprofloxacin in serum.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy (Teratogenic Effects. Pregnancy Category C)

There are no adequate and well-controlled studies of Proquin XR in pregnant women. However, human data on more than 500 infants from two controlled cohort studies do not show an increased risk for major congenital malformations overall in infants exposed to ciprofloxacin during the first trimester of pregnancy or at other times during pregnancy. The risks to a developing musculoskeletal system were not fully evaluated. Animal studies in rats and rabbits demonstrated variations or anomalies in fetal skeletal development and increased embryo-fetal mortality. These effects occurred at clinically relevant doses but also in the presence of maternal toxicity. Proquin XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A controlled, prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. Following in-utero exposure to fluoroquinolones during embryogenesis, there was no associated 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. Rates of spontaneous abortions, prematurity and low birth weight did not differ between the study groups, and there were no clinically significant musculoskeletal dysfunctions up to one year of age in ciprofloxacin exposed children.

A controlled, retrospective cohort study of more than 30,000 infants enrolled in Medicaid included 588 infants exposed to ciprofloxacin during pregnancy (average 8 day exposure), and 439 exposures occurred during the first trimester. Compared to a control group with no antibiotic exposure and a control group with exposure to a nonteratogenic antibiotic commonly used during pregnancy, infants exposed to ciprofloxacin during the first trimester (or other times during pregnancy) did not demonstrate an increased risk for major congenital malformations overall. The study was powered to rule out a two fold increased risk for major malformations. The study was not designed to fully assess abnormal musculoskeletal development.

Another prospective observational 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 the background rates for congenital malformations in the general population. There was no specific patterns of congenital abnormalities and no clear adverse reactions due to in-utero exposure to ciprofloxacin.

Published data do not suggest increased rates of prematurity, spontaneous abortions, or birth weight in women exposed to ciprofloxacin during pregnancy, but these data are very limited.

In embryo/fetal developmental toxicity studies, pregnant rats and rabbits received oral doses of ciprofloxacin up to 600 mg/kg/day in rats and 30 mg/kg/day in rabbits. In rats, fetal skeletal variations occurred 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). In pregnant rabbits, the maternally toxic 30 mg/kg/day dose resulted in abortions and reductions in body weight gain. Embryo/fetal lethality and skeletal developmental effects also occurred in rabbits at this dose level (approximately 1.2-fold the recommended therapeutic dose based upon body surface area), while the maternally toxic 10 mg/kg/day dose level did not induce embryo/fetal developmental effects. A peri/postnatal developmental toxicity study conducted in pregnant/lactating female rats exhibited no developmental effects in offspring at the highest dose level of 600 mg/kg/day. Both the 300 and 600 mg/kg/day dose levels were maternally toxic to the pregnant dams based upon slight body weight gain reduction. There was no evidence of compound-related fetal malformation in any of the reproductive toxicity studies.

8.3 Nursing Mothers

Ciprofloxacin is excreted in human milk. In one study, ten lactating women received oral ciprofloxacin 750 mg every 12 hours. Peak human milk concentrations of ciprofloxacin following the third dose averaged 3.79 mcg/mL (S.D. 1.26), and these levels decreased to a mean of 0.02 mcg/mL at 24 hours after the third dose. Based on these concentrations, the maximum daily infant dose of ciprofloxacin through human milk is about 0.569 mg/kg per day, about 2.8% of the approved 20 mg/kg dose in children one year of age or older.

Because of the potential for serious adverse reactions in infants from ciprofloxacin, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of ciprofloxacin to the mother. During short courses of therapy, nursing mothers may express and discard milk. Human milk feeding can resume 24 hours after the last dose of Proquin XR.

8.4 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 *Nonclinical Toxicology (13.2)*]

8.5 Geriatric Use

Geriatric patients 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. 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 Proquin XR to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to

discontinue Proquin XR and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [see *Warnings and Precautions (5.1), Adverse Reactions (6)*].

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* (12.3)].

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).

8.6 Renal Impairment

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 mild to moderate renal impairment. The efficacy of Proquin XR has not been studied in patients with severe renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dosage adjustment is required with Proquin XR in patients with stable chronic cirrhosis. However, the pharmacokinetics of ciprofloxacin in patients with acute hepatic impairment has not been fully elucidated [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

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.

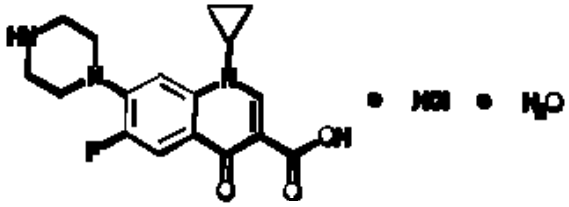
Serious adverse effects were not observed in rats receiving single oral doses of ciprofloxacin as high as 2,000 mg/kg.

11 DESCRIPTION

Proquin XR (ciprofloxacin hydrochloride monohydrate) extended-release tablets contain 582 mg of ciprofloxacin hydrochloride monohydrate, a synthetic broad-spectrum fluoroquinolone antimicrobial agent for oral administration, which is equivalent to 500 mg of ciprofloxacin.

Ciprofloxacin hydrochloride monohydrate is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate. The molecular weight of

the ciprofloxacin hydrochloride 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 hydrochloride monohydrate equivalent) tablets, utilizing AcuForm® delivery technology. Proquin XR tablets are blue film-coated and oval-shaped. The inactive ingredients are povidone, magnesium stearate, polyethylene oxide, and film coating (Opadry® Blue).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents [see *Clinical Pharmacology, Microbiology (12.4)*].

12.3 Pharmacokinetics

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 $AUC_{0\text{-}24h}$ 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. Table 2 presents the pharmacokinetic parameters obtained at steady state for Proquin XR 500 mg once daily versus ciprofloxacin immediate-release tablets 250 mg twice daily.

Table 2: 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 ciprofloxacin immediate-release tablets twice daily.
C_{max2} = peak concentration after the morning dose of ciprofloxacin immediate-release tablets twice daily.
[c] T_{max1} = time of peak concentration after the evening dose ciprofloxacin immediate-release tablets twice daily.
T_{max2} = time of peak concentration after the morning dose ciprofloxacin immediate-release tablets twice daily.

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 once daily and ciprofloxacin immediate-release tablets 250 mg twice daily are shown in Table 3.

Table 3: 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)
Ciprofloxacin immediate-release tablets 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.

Specific 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 *Use in Specific Populations (8.5)*].

Renal Impairment: After receiving a single dose of Proquin XR 500 mg, the ciprofloxacin AUC_{0-24h} 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 *Use in Specific Populations (8.6)*].

Hepatic Impairment: 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 *Use in Specific Populations (8.7)*].

Pediatrics: The pharmacokinetics of Proquin XR have not been studied in pediatric populations [see *Use in Specific Populations (8.4)*].

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 Cmax 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, Cmax 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 *Drug Interactions (7.2)*].

Histamine H2-receptor antagonists: Histamine H2-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.

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. 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.

Warfarin: The co-administration of single doses of Proquin XR and warfarin (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, the pharmacologically active enantiomer, were not significantly altered by ciprofloxacin co-administration, the half-life of R-warfarin was statistically significantly prolonged (P=0.029). When Proquin XR and oral anticoagulants are administered concomitantly, prothrombin time or other suitable coagulation tests should be monitored [see *Drug Interactions (7.4)*].

12.4 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 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 $1x10^{-6}$.

Activity *in vitro* and *in vivo*

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. 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 (1)* section.

Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella pneumoniae

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

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 criteria outlined in Table 4.
- **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 f criteria outlined in Table 4. 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.

Table 4: Susceptibility Interpretive Criteria for Ciprofloxacin

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤1	2	≥4	≥21	16-20	≤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 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.

- **Quality Control:**
  Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard ciprofloxacin powder should give the MIC values provided in Table 4. For diffusion technique, the 5 mcg ciprofloxacin disk should provide zone diameters provided in Table 5.

Table 5: Quality Control for Susceptibility Testing

Microorganism	Microorganism QC Number	MIC (mcg/mL)	Disk Diffusion (zone diameter in mm)
Escherichia coli	ATCC 25922	0.004-0.015	30-40
Staphylococcus aureus	ATCC 29213	0.12-0.5	Not applicable
Staphylococcus aureus	ATCC 25923	Not applicable	22 – 30

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 Animal Pharmacology

Gastrointestinal or other toxic effects were not observed in male and female beagle dogs following oral administration of Proquin XR tablets at doses up to 1,000 mg/day for 28 consecutive days (approximately 3 and 5 times the human therapeutic dose based upon AUC comparisons to male and female dogs, respectively).

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested [see *Warnings and Precautions (5.8)* and *Use in Specific Populations (8.4)*].

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 [see *Adverse Reactions (6.1)*].

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 [see *Drug Interactions (7.9)*].

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.

14 CLINICAL STUDIES

14.1 Uncomplicated Urinary Tract Infections

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. 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 control 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 Table 6.

Table 6: Bacteriological Eradication and Clinical Cure Rates at the Test-of-Cure (TOC) Visit

	Proquin XR 500 mg once daily for 3 days	**Ciprofloxacin immediate-release tablet 250 mg twice daily for 3 days**
	qd x 3 Days	**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 ciprofloxacin immediate-release tablets. Of the patients with their baseline organism eradicated, new infections were detected in 42/254 (16%) Proquin XR-treated patients and 32/225 (14%) ciprofloxacin-treated patients at the TOC visit. Gram-negative rods were responsible for new infections in 10 Proquin XR-treated patients and 7 ciprofloxacin-treated patients, and Enterococcus species were isolated in 24 Proquin XR-treated patients, and 20 ciprofloxacin-treated patients.

15 REFERENCES

Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Eight Edition. Approved Standard CLSI Document M7-A8, Vol. 29, No. 2, CLSI, Wayne, PA, January, 2009.

Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests. Tenth Edition. Approved Standard CLSI Document M2-A10, Vol. 29, No. 1, CLSI, Wayne, PA, January, 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

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	13913-001-30

Blister Packs of 3: 500 mg 13913-001-03

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

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Medication Guide*

17.1 Use Only for Uncomplicated Urinary Tract Infection

Inform patients that Proquin XR is only approved to treat uncomplicated urinary tract infections and to contact their healthcare provider if they do not feel better or if they develop fever and back pain while or after taking Proquin XR.

17.2 Tendon Disorders

Instruct patients 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 Proquin XR treatment. The risk of severe tendon disorders 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 [see *Boxed Warning and Warnings and Precautions (5.1)*].

17.3 Myasthenia Gravis Syndrome

Fluoroquinolones like Proquin XR may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if you have any worsening muscle weakness or breathing problems.

17.4 Hypersensitivity

Inform patients that ciprofloxacin may be associated with hypersensitivity reactions; even following a single dose. Instruct patients to discontinue Proquin XR and contact their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction [see *Warnings and Precautions (5.2)*].

17.5 Convulsions

Inform patients that **c**onvulsions have been reported in patients taking fluoroquinolones, including ciprofloxacin and to notify their physician before taking this drug if they have a history of convulsions [*see Warnings and Precautions (5.5)*].

17.6 Neurologic Adverse Effects (e.g., dizziness, lightheadedness)

Instruct patients to wait to see how they react to Proquin XR before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination [see *Warnings and Precautions (5.5)*].

17.7 *Clostridium difficile*-Associated Diarrhea

Inform patients 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, instruct patients to contact their physician as soon as possible [see *Warnings and Precautions (5.6)*].

17.8 Peripheral Neuropathies

Advise patients if symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physician [see *Warnings and Precautions (5.7)*].

17.9 Photosensitivity

Advise to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking Proquin XR. If patients need to be outdoors when taking Proquin XR, instruct them to 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, instruct patients to contact their physician [see *Warnings and Precautions (5.9)*].

17.10 Administration with Food, Fluids, and Concomitant Medications

Instruct patients to:

- Take Proquin XR with a main meal of the day, preferably the evening meal and not to take more than one Proquin XR tablet per day, even if a dose is missed.
- Take Proquin XR tablets whole. Never split, crush, or chew tablets.
- Drink fluids liberally while taking Proquin XR to avoid formation of a highly concentrated urine and crystal formation in the urine.
- Take Proquin XR at least 4 hours before or 2 hours after antacids and other multivalent cation-containing products. 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 reduces the absorption of ciprofloxacin.
- Avoid taking Proquin XR with dairy products (like milk or yogurt) or calcium-fortified juices alone, since the absorption of ciprofloxacin may be significantly reduced by these products. However, Proquin XR may be taken with a meal that contains these products.

17.11 Drug Interactions

Instruct patients to inform their healthcare provider if they are taking theophylline. Proquin XR may increase the effects of theophylline and some other prescription or over-the-counter medications, when taken concurrently with ciprofloxacin.

Instruct patients to inform their healthcare provider if they are taking antacids and other multivalent cation containing prescription or over-the-counter medications. Such products can reduce the absorption of ciprofloxacin [see *Administration with Food, Fluids and Concomitant Medications* (17.9)].

17.12 Use of Proquin XR Sample Pack

Advise the patient that the sample pack contains only one dose for the first day of treatment with Proquin® XR. Complete treatment requires 3 doses. The patient must fill a prescription for the remaining two doses.

17.13 Human Milk Feeding

Advise women to avoid feeding their infants with their milk during treatment with Proquin XR. Women should either discontinue feeding or pump and discard their milk during treatment and for 24 hours after the last dose *[see Use in Specific Populations (8.3)]*.

17.14 Antibacterial Resistance

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 [see *Warnings and Precautions (5.10)*].

PROQUIN® XR (pro-kwin)
(Ciprofloxacin)
Extended-Release Tablets

Read the Medication Guide that comes with Proquin® XR 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 Proquin® XR?

Proquin® XR belongs to a class of antibiotics called fluoroquinolones. Proquin® XR 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, and talk with your healthcare provider about whether you should continue to take Proquin® XR.

Tendon rupture or swelling of the tendon (tendonitis)

- Tendons are the tough cords of tissue that connects muscles to bones.
- Pain, swelling, inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including Proquin® XR. The risk of getting tendon problems is higher if you:
    - are over 60 years of age
    - are taking steroids (corticosteroids)
    - have had a kidney, heart or lung transplant

- Swelling of the tendon (tendonitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
- Other reasons for tendon ruptures 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 Proquin® XR 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 Proquin® XR**.** 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 Proquin® XR. 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 incident in a tendon area
    - unable to move the affected area or bear weight
- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like **Proquin XR** 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 Proquin® XR?**" for more information about side effects.

What is Proquin® XR?

Proquin® XR is a fluoroquinolone antibiotic medicine used to treat simple bladder infections caused by certain germs called bacteria.

It is not known if Proquin® XR is safe and works in treating any infections other than simple bladder infections.

It is also not known if Proquin® XR is safe and works in children under 18 years of age.

Children have a higher chance of getting bone and joint (musculoskeletal) problems while taking fluoroquinolone antibiotic medicines.

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

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

Who should not take Proquin® XR?

Do not take Proquin® XR 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 Proquin® XR. Ask your healthcare provider if you are not sure. See the complete list of ingredients in Proquin® XR at the end of this Medication Guide.

What should I tell my healthcare provider before taking Proquin® XR?

See "**What is the most important information I should know about Proquin® XR**?"

Before taking Proquin® XR, tell your healthcare provider if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have a history of seizures
- have kidney problems
- have low blood potassium (hypokalemia)
- 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 Proquin® XR will harm your unborn child.
- are breast-feeding or planning to breast-feed. Proquin® XR can pass into your breast milk and may harm your baby. You and your healthcare provider should decide whether you will take Proquin® XR or breastfeed. You should not do both. See "What should I avoid while taking Proquin XR?"

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

- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®). Serious reactions, including death can happen in people who take Proquin XR and theophylline. Your healthcare provider may change your dose of theophylline and perform blood test to check your theophylline level if you take Proquin XR and theophylline.
- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take Proquin® XR or other

fluoroquinolones may increase your risk of central nervous system effects and seizures. See **"What are the possible side effects of Proquin® XR?"**

- a blood thinner (warfarin, Coumadin, Jantoven)
- glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®)
- phenytoin (Fosphenytoin Sodium®, Cerebyx®, Dilantin-125®, Dilantin, Extended Phenytoin Sodium®, Prompt Phenytoin Sodium®, Phenytek®)
- products that contain caffeine
- a medicine to control your heart rate or rhythm (antiarrhythmics). See "**What are the possible side effects of Proquin® XR?"**
- 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 Proquin® XR?**"
- methotrexate (Trexall®)
- probenecid (Col-probenecid®)
- cyclosporine (Gengraf®, Sandimmune®, Neoral®)
- Certain medicines may keep Proquin® XR from working correctly. Take Proquin® XR at least 4 hours before or 2 hours after taking these products.
    - an antacid, multivitamin, or other product that contains magnesium, calcium, 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.

What if I receive a sample of Proquin® XR from my healthcare provider?

This sample contains only 1 dose for the first day of treatment of Proquin® XR and is not a complete treatment. To treat your bladder infection, you must take all 3 daily doses of Proquin® XR. You must fill a prescription from your healthcare provider for the remaining two daily doses before your next scheduled dose. Take all of your doses as prescribed by your healthcare provider, even if you are feeling better after the first dose. If you stop taking Proquin® XR before all of your doses are complete, Proquin® XR may not cure your bladder infection. It is not known if Proquin® XR will treat infections other than bladder infections. See also "**How should I take Proquin® XR?**"

How should I take Proquin® XR?

- Take Proquin® XR exactly as prescribed by your healthcare provider.
- Proquin® XR should be taken by mouth one time each day for 3 days
- Take Proquin® XR with your main meal of the day, preferably the evening meal. Try to take Proquin® XR at about the same time each day.
- Swallow Proquin® XR tablets whole. Do not split, crush, or chew Proquin® XR tablets**.** Tell your healthcare provider if you can not swallow the tablets whole. Your healthcare provider will prescribe a different medicine for you.
- Drink plenty of fluids while taking Proquin® XR**.**
- 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.
- Proquin® XR does not work as well if you take it without a meal.
- Do not skip any doses, or stop taking Proquin® XR 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 Proquin® XR?**")
    - you have a serious allergic reaction (see "**What are the possible side effects of Proquin® XR**?"), 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 Proquin® XR. If this happens, Proquin® XR and other antibiotic medicines may not work in the future.
- Tell your healthcare provider if you do not feel better or if you get fever and back pain, while you are taking Proquin® XR or after you finish taking it. This may mean that your infection has not been cured and you may need another antibiotic medicine to treat your infection.
- If you miss a dose of Proquin® XR, take it as soon as your remember. Do not take more than one Proquin® XR tablet a day, even if you miss a dose.
- If you take too much, call your healthcare provider or get medical help right away.

What should I avoid while taking Proquin® XR?

- Proquin® XR 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 Proquin® XR affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. Proquin® XR can make your skin sensitive to the sun (photosensitivity) and the light from the sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking Proquin® XR, call your healthcare provider right

- Avoid breastfeeding during treatment with Proquin XR. If you are breastfeeding, you should either stop breastfeeding, or pump and throw away the milk **during treatment and for 24 hours after your last dose** of Proquin XR. See "What should I tell my doctor before taking Proquin XR?"

What are the possible side effects of Proquin® XR?

Proquin® XR can cause side effects that may be serious or even cause death.

- See "**What is the most important information I should know about Proquin® XR?**"
- **Serious allergic reactions**. Allergic reactions can happen in people taking fluoroquinolones, including Proquin® XR, even after only one dose. Stop taking Proquin® XR and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
    - rash or blistering and break down of your skin
    - trouble breathing or swallowing
    - swelling of the lips, tongue, face
    - throat tightness, hoarseness
    - rapid heartbeat
    - seizures
    - yellowing of the skin or eyes. Stop taking Proquin® XR and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to Proquin® XR (a liver problem).
    - shortness of breath, tiredness, unexplained bruising and bleeding.
- **Central Nervous System Effects:** Seizures can happen in people who take fluoroquinolone antibiotics, including Proquin® XR. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking Proquin® XR will change your risk of having a seizure. Seizures have been reported in patients taking fluoroquinolone antibiotics including Proquin® XR.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of Proquin® XR. 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 lightheadedness
- feel more suspicious (paranoia)
- suicidal thoughts or acts

- **Intestine infection** (Pseudomembranous colitis)**.** Pseudomembranous colitis can happen with most antibiotics, including Proquin® XR. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including Proquin® XR. 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

  Proquin® XR may need to be stopped to prevent nerve damage.
- **Sensitivity to sunlight** (photosensitivity). See "**What should I avoid while taking Proquin® XR?"**
- **Low blood sugar** (hypoglycemia). People taking fluoroquinolone medicines such as Proquin® XR with oral anti-diabetes medicines glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®) can get low blood sugar (hypoglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. Tell your healthcare provider if you get low blood sugar with Proquin® XR. Your antibiotic medicine may need to be changed.

The most common side effects of Proquin® XR include:

- yeast infection
- inflamed nose and throat
- headache
- feeling an urgent need to urinate

These are not all the possible side effects of Proquin® XR. 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 Proquin® XR?

- Store Proquin® XR at 59 ºF to 86ºF (15ºC to 30ºC).

Keep Proquin® XR and all medicines out of the reach of children.

General information about Proquin® XR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Proquin® XR for a condition for which it is not prescribed. Do not share Proquin® XR with other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Proquin® XR. If you would like more information about Proquin® XR, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Proquin® XR that is written for healthcare professionals. For more information go to www.proquinxr.com or call 1-866-458-6389.

What are the ingredients in Proquin® XR?

- Active ingredient: ciprofloxacin hydrochloride monohydrate
- Inactive ingredient: povidone, magnesium stearate, polyethylene oxide and film coating (Opadry Blue)

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Rx Only

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