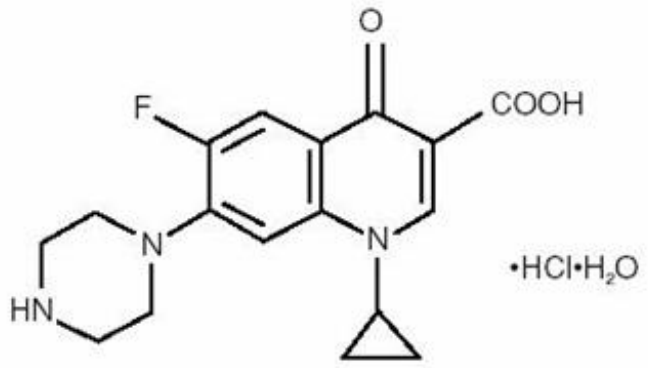
CIPROFLOXACIN- ciprofloxacin solution
REMEDYREPACK INC.

Ciprofloxacin ophthalmic solution USP0.3%

Sterile

DESCRIPTION

Ciprofloxacin ophthalmic solution is a synthetic, sterile, multiple dose, antimicrobial for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. It is a faint to light yellow crystalline powder with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:



Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Each mL of Ciprofloxacin ophthalmic solution 0.3% contains: **Active:** ciprofloxacin HCl 3.5 mg equivalent to 3 mg base. **Preservative:** benzalkonium chloride 0.006%. **Inactives:** sodium acetate, acetic acid, mannitol 4.6%, edetate disodium 0.05%, hydrochloric acid and/or sodium hydroxide (to adjust pH) and water for injection. The pH is approximately 4.5 and the osmolality is approximately 300 mOsm.

CLINICAL PHARMACOLOGY

Systemic Absorption: A systemic absorption study was performed in which Ciprofloxacin ophthalmic solution 0.3% was administered in each eye every two hours while awake for two days followed by every four hours while awake for an additional 5 days. The maximum reported plasma concentration of ciprofloxacin was less than 5

ng/mL. The mean concentration was usually less than 2.5 ng/mL.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Aerobic gram-Positive microorganisms:

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Streptococcus pneumoniae

Streptococcus (Viridans Group)

Aerobic gram-negative microorganisms:

Haemophilus influenzae

Pseudomonas aeruginosa

Serratia marcescens

Ciprofloxacin has been shown to be active *in vitro* against most strains of the following organisms, however, *the clinical significance of these data is unknown:*

Gram-Positive:

Enterococcus faecalis (Many strains are only moderately susceptible)

Staphylococcus haemolyticus

Staphylococcus hominis

Staphylococcus saprophyticus

Streptococcus pyogenes

Gram-Negative

Acinetobacter calcoaceticus subsp. anitratus

Aeromonas caviae

Aeromonas hydrophila

Brucella melitensis

Campylobacter coli

Campylobacter jejuni

Citrobacter diversus

Citrobacter freundii

Edwardsiella tarda

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus ducreyi

Haemophilus parainfluenzae

Kiebsiella pneumoniae

Klebsiella oxytoca

Legionella pneumophila

Moraxella (Branhamella) catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Neisseria meningitides

Pasteurella multocida

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Salmonella enteritidis

Salmonella typhi

Shigella sonneii

Shigella flexneri

Vibrio cholera

Vibrio parahaemolyticus

Vibrio vulnificus

Yersinia enterocolitica

Other Organisms:

Chlamydia trachomatis (only moderately susceptible) and *Mycobacterium tuberculosis* (only moderately susceptible).

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

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible

to ciprofloxacin.

INDICATIONS AND USAGE

Ciprofloxacin ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Corneal Ulcers:

Pseudomonas aeruginosa

Serratia marcescens *

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus (Viridans Group) *

Conjunctivitis:

Haemophilus influenzae

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus pneumoniae

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Remove contact lenses before using.

PRECAUTIONS

General:

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24 to 72 hours), in five patients, resolution was noted in 10 to 13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations, 18 to 44 days after onset of the event, complete resolution of the precipitate was noted. In three patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (see ADVERSE REACTIONS).

Information for patients:

Do not touch dropper tip to any surface, as this may contaminate the solution.

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(724) 465-8762

Drug Interactions:

Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

- *Salmonella* /Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V $_{79}$Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)

- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:
- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to two years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose.After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no mbryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women. Ciprofloxacin ophthalmic solution 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether topically applied ciprofloxacin is excreted in human milk. However, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when Ciprofloxacin ophthalmic solution 0.3% is administered to a nursing mother.

Pediatric Use:

The safety and effectiveness of Ciprofloxacin ophthalmic solution 0.3% have been established in all ages. Use of Ciprofloxacin ophthalmic solution is supported by evidence from adequate and well controlled studies of Ciprofloxacin ophthalmic solution in adults, children and neonates [see Clinical Studies]. Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

Geriatric Use:

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported drug related adverse reaction was local burning or

discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (see PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

OVERDOSAGE

A topical overdose of Ciprofloxacin ophthalmic solution 0.3% may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION

Corneal Ulcers:

The recommended dosage regimen for the treatment of **corneal ulcers** is two drops into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. On the third through the fourteenth day, place two drops in the affected eye every four hours. Treatment may be continued after 14 days if corneal re-epithelialisation has not occurred.

Bacterial Conjunctivitis:

The recommended dosage regimen for the treatment of **bacterial conjunctivitis** is one or two drops instilled into the conjunctival sac(s) every two hours while awake for two days and one or two drops every four hours while awake for the next five days.

HOW SUPPLIED

As a sterile ophthalmic solution: 2.5 mL, 5 mL and 10 mL in translucent LDPE bottle with insert cap assembly comprising of a tan colored HDPE screw cap over a LDPE nozzle with tamper evident LDPE dust cover sealing the bottle cap.

NDC: 70518-2390-00

PACKAGING: 1 in 1 CARTON, 5 mL in 1 BOTTLE PLASTIC TYPE 0

STORAGE:

Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature]. Retain in carton until contents are used and protect from light.

ANIMAL PHARMACOLOGY:

Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one month topical ocular study using immature Beagle dogs did not demonstrate any articular

lesions.

CLINICAL STUDIES:

Following therapy with Ciprofloxacin ophthalmic solution 0.3%, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialisation occurred in about 92% of the ulcers.

In 3 and 7 day multicenter clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70-80% had all causative pathogens eradicated by the end of treatment.

In a randomized, double-masked, multicenter, parallel-group clinical trial of pediatric patients with bacterial conjunctivitis, between birth and 31 days of age, patients were dosed with Ciprofloxacin ophthalmic solution or another anti-infective agent. Clinical outcomes for the trial demonstrated a clinical cure rate of 80% at Day 9 and a microbiological eradication success rate of 85% at Day 9.

Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

Rx Only

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Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

DRUG: ciprofloxacin

GENERIC: Ciprofloxacin

DOSAGE: SOLUTION

ADMINSTRATION: OPHTHALMIC

NDC: 70518-2390-0

PACKAGING: 5 mL in 1 BOTTLE, PLASTIC

OUTER PACKAGING: 1 in 1 CARTON

ACTIVE INGREDIENT(S):
- CIPROFLOXACIN HYDROCHLORIDE 3mg in 1mL

INACTIVE INGREDIENT(S):
- SODIUM ACETATE ANHYDROUS
- ACETIC ACID
- MANNITOL
- EDETATE DISODIUM
- BENZALKONIUM CHLORIDE
- SODIUM HYDROXIDE
- HYDROCHLORIC ACID

Ciprofloxacin

0.3 %

Ophthalmic Solution

QTY: 5 mL

For topical ophthalmic use only; Sterile

remedy repack

RX ONLY

NDC #: 70518-2390-00

Expires:

LOT #:

Source NDC: 69315-0308-05

MFG: Leading, Fairfield, NJ 07004

Keep this and all medication out of the reach of children

WARNING: Do not touch dropper tip to any surface, as this may contaminate the solution.

Directions For Use: See Package Insert

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

Repackaged by: RemedyRepack Inc., Indiana, PA 15701, 724.465.8762

CIPROFLOXACIN

ciprofloxacin solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70518-2390(NDC:69315-308)
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CIPROFLOXACIN HYDROCHLORIDE (UNII: 4BA73M5E37) (CIPROFLOXACIN - UNII:5E8K9I0O4U)	CIPROFLOXACIN	3 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM ACETATE ANHYDROUS (UNII: NVG71ZZ7P0)	
ACETIC ACID (UNII: Q40Q9N063P)	
MANNITOL (UNII: 3OWL53L36A)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:70518-2390-0	1 in 1 CARTON	10/25/2019	

1		5 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077568	10/25/2019	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 2/2024 REMEDYREPACK INC.