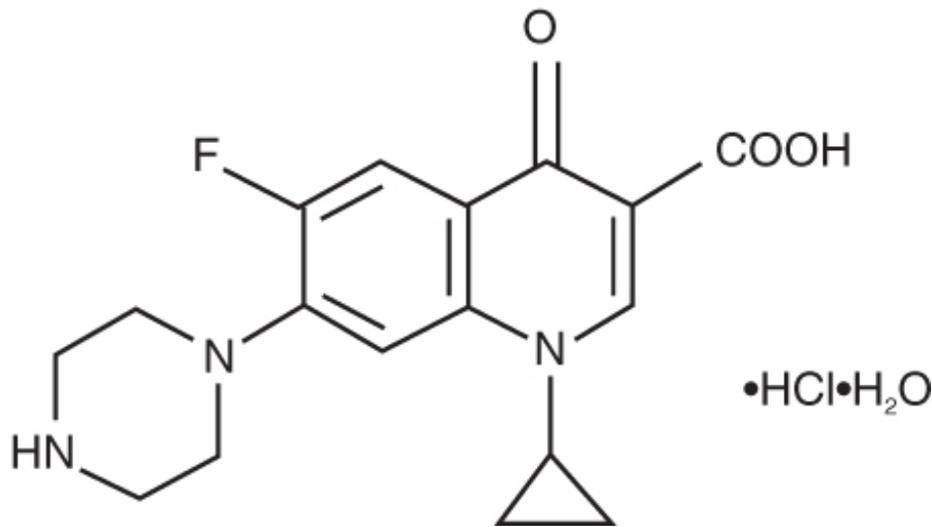


CIPROFLOXACIN HYDROCHLORIDE- ciprofloxacin hydrochloride solution/ drops
Aidarex Pharmaceuticals LLC

Ciprofloxacin Hydrochloride Ophthalmic Solution
0.3% as base
Sterile

DESCRIPTION

Ciprofloxacin Hydrochloride 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 Hydrochloride Ophthalmic Solution contains: **Active:** ciprofloxacin HCl 3.5 mg equivalent to 3 mg base. **Preservative:** benzalkonium chloride 0.006%. **Inactive:** sodium acetate, acetic acid, mannitol 4.6%, edetate disodium 0.05%, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water. 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 Hydrochloride Ophthalmic Solution 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 section).

Gram-Positive:

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus (Viridans Group)

Gram-Negative:

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

Klebsiella pneumoniae

Klebsiella oxytoca

Legionella pneumophila

Moraxella (Branhamella) catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Neisseria meningitidis

Pasteurella multocida

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Salmonella enteritidis

Salmonella typhi

Shigella sonnei

Shigella flexneri

Vibrio cholerae

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.

Clinical Studies:

Following therapy with Ciprofloxacin Hydrochloride Ophthalmic Solution, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization 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.

INDICATIONS AND USAGE

Ciprofloxacin Hydrochloride 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 24-72 hours), in five patients, resolution was noted in 10-13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations, 18-44 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.

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 V79 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

Pregnancy Category C: 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 embryotoxicity or teratogenicity was observed. There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin Hydrochloride Ophthalmic Solution 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 Hydrochloride Ophthalmic Solution is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 1 year have not been established.

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.

OVERDOSAGE

A topical overdose of Ciprofloxacin Hydrochloride Ophthalmic Solution 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-epithelialization 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 in Alcon's DROP-TAINER** dispensing system consisting of a natural low density polyethylene bottle and dispensing plug and tan polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 mL

STORAGE: Store at 2° to 25°C (36° to 77°F). 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.

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc., at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Rx Only

Rev. May 2012

**DROP-TAINER is a registered trademark of Alcon Research, Ltd.

9007230-1011

SANDOZ

Manufactured by
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 for
Sandoz Inc.
Princeton, NJ 08540
Printed in USA

Repackaged by:
Aidarex Pharmaceuticals, LLC
Corona, CA 92880 USA

PRINCIPAL DISPLAY PANEL

Repackaged by:
Aidarex Pharmaceuticals, LLC
Corona, CA 92880 USA

NDC 33261-0910

Ciprofloxacin Hydrochloride Ophthalmic Solution, 0.3% as base

0.3%

Rx only

STERILE

2.5 ml

SANDOZ

FOR TOPICAL OPHTHALMIC USE ONLY.

INGREDIENTS: Each mL contains:

Active: ciprofloxacin HCl 3.5 mg equivalent to 3 mg base.

Preservative: benzalkonium chloride 0.006%.

Inactives: sodium acetate, acetic acid, mannitol, edetate disodium, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

USUAL DOSAGE: Read insert.

STORAGE: Store at 2° to 25°C (36° to 77°F).
Protect from light.

Manufactured by
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 for
Sandoz Inc.
Princeton, NJ 08540

Rev. 05/2012

H13234-1213



33261-0910_CIPROFLOXACIN_2.5ML

CIPROFLOXACIN HYDROCHLORIDE

ciprofloxacin hydrochloride solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:33261-910(NDC:61314-656)
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CIPROFLOXACIN HYDROCHLORIDE (UNII: 4BA73M5E37) (CIPROFLOXACIN - UNII:5E8K9J0O4U)	CIPROFLOXACIN	3 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
SODIUM ACETATE (UNII: 4550K0SC9B)	
ACETIC ACID (UNII: Q40Q9N063P)	

MANNITOL (UNII: 3OWL53L36A)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0K00R)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:33261-910-01	2.5 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	04/03/2018	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA019992	04/03/2018	

Labeler - Aidarex Pharmaceuticals LLC (801503249)

Establishment			
Name	Address	ID/FEI	Business Operations
Aidarex Pharmaceuticals		801503249	RELABEL(33261-910)

Revised: 8/2018

Aidarex Pharmaceuticals LLC