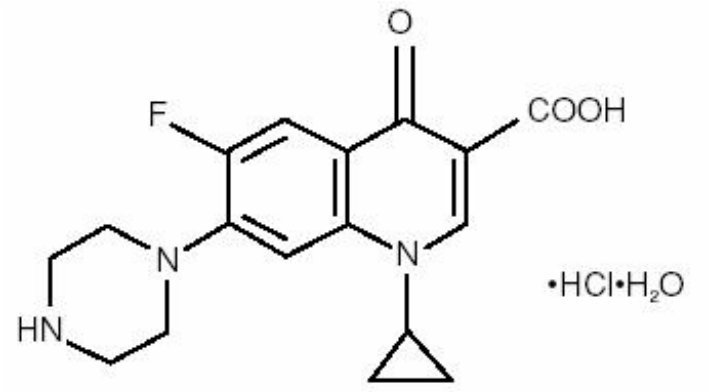
CIPROFLOXACIN - ciprofloxacin solution/ drops
Pack Pharmaceuticals, LLC

Ciprofloxacin Ophthalmic SolutionUSP
0.3% as base

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 $C_{17}H_{18}FN_3O_3$•HCl•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 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 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 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 sonneii

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 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 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 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

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 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 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 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: 5 mL and 10 mL mLin translucent LDPE plastic ophthalmic dispensers with a tan polystyrene cap

5 mL - **NDC** 16571-135-50

10 mL - **NDC** 16571-135-10

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.

Rx Only

Distributed by:
PACK Pharmaceuticals, LLC
1110 W.Lake Cook Rd., Ste 152 Buffalo Grove,
IL60089

Manufactured by
FDC Limited
B-8, M.I.D.C. Waluj, Dist. Aurangabad 431 136
Maharashtra State, India

Revision 07/10

STERILE OPHTHALMIC SOLUTION CIPROFLOXACIN OPHTHALMIC SOLUTION USP

INSTRUCTIONS FOR USE

Please follow these instructions carefully when using Ciprofloxacin ophthalmic solution. Use Ciprofloxacin ophthalmic solution as prescribed by your doctor.

1. If you use other topically applied ophthalmic medications, they should be administered at least 10 minutes before or after the use of Ciprofloxacin ophthalmic solution.
2. Wash hands before each use.
3.

Bottle as received.

Tighten the cap on the nozzle till the cap touches the shoulder.

4.

The spike in the cap will pierce the tip of the bottle. To open the bottle unscrew the cap

5.

Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.
Invert the bottle and press lightly until a single drop is dispensed into the eye as directed by your doctor.
Do not touch your eye or eyelid with the dropper tip.
Repeat step 5 with the other eye if instructed to do so by your doctor.

6.

Replace the cap on the bottle.
Do not overtighten the cap.

7. OPHTHALMIC MEDICATIONS, IF HANDLED IMPROPERLY, CAN BECOME CONTAMINATED BY COMMON BACTERIA KNOWN TO CAUSE EYE INFECTIONS. SERIOUS DAMAGE TO THE EYE AND SUBSEQUENT LOSS OF VISION MAY RESULT FROM USING CONTAMINATED OPHTHALMIC MEDICATIONS. IF YOU THINK YOUR MEDICATION MAY BE CONTAMINATED, OR IF YOU DEVELOP AN EYE INFECTION, CONTACT YOUR DOCTOR IMMEDIATELY CONCERNING CONTINUED USE OF THIS BOTTLE
8. The dispenser tip is designed to provide a premeasured drop; therefore, do NOT enlarge the hole

of the dispenser tip.

9. After you have used all doses, there will be some ciprofloxacin left in the bottle. You should not be concerned since an extra amount of ciprofloxacin has been added and you will get the full amount of ciprofloxacin that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

WARNING: KEEP OUT OF REACH OF CHILDREN.
IF YOU HAVE ANY QUESTIONS ABOUT THE USE OF CIPROFLOXACIN OPHTHALMIC SOLUTION, PLEASE CONSULT YOUR DOCTOR.

5 mL Carton Label

NDC 16571-135-50

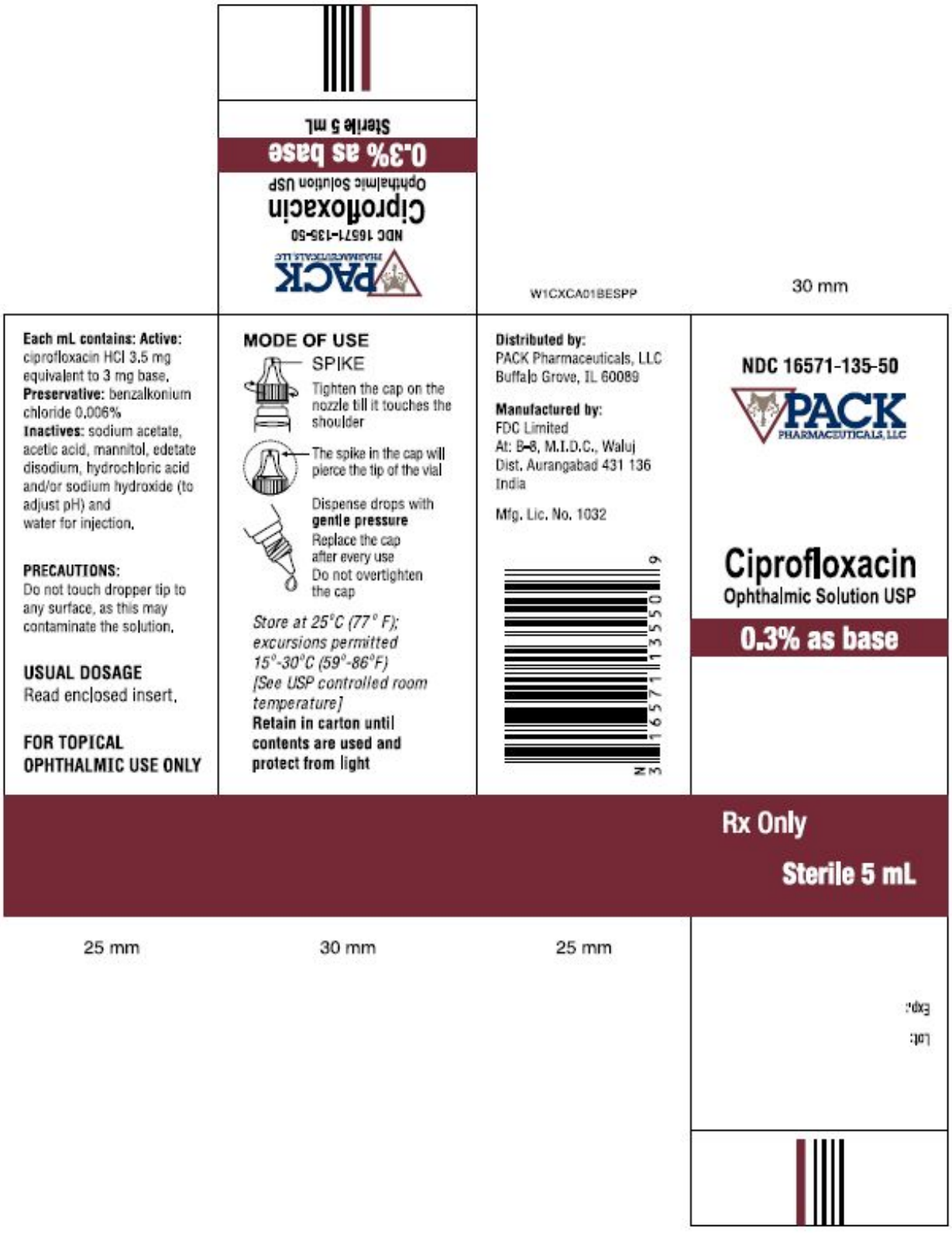
PACK PHARMACEUTICALS, LLC

Ciprofloxacin
Ophthalmic Solution USP

0.3% as base

Rx Only

Sterile 5 mL



CIPROFLOXACIN

ciprofloxacin solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16571-135
Route of Administration	OPHTHALMIC, TOPICAL		

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**
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
ACETIC ACID (UNII: Q40Q9N063P)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM ACETATE (UNII: 4550K0SC9B)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:16571-135-50	1 in 1 CARTON		
1		5 mL in 1 BOTTLE, PLASTIC		
2	NDC:16571-135-10	1 in 1 CARTON		
2		10 mL in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077568	09/15/2010	

Labeler - Pack Pharmaceuticals, LLC (614823875)

Registrant - FDC Limited (650078413)

Establishment

Name	Address	ID/FEI	Business Operations
FDC Limited		862267994	analysis, manufacture

Revised: 7/2010 Pack Pharmaceuticals, LLC