PRODUCT MONOGRAPH

NU-CIPROFLOX
Ciprofloxacin Ophthalmic Solution USP

0.3% w/v
(ciprofloxacin, as ciprofloxacin hydrochloride monohydrate)

Antibacterial Agent

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THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTIONS AND CLINICAL PHARMACOLOGY

The bactericidal action of ciprofloxacin results from inhibition of the enzyme, DNA gyrase, which is required for the synthesis of bacterial DNA.

Pharmacokinetics

Topically applied ciprofloxacin ophthalmic solution is absorbed systemically with ciprofloxacin plasma concentrations approaching steady state at the end of dosing each day. Ciprofloxacin plasma concentrations following a routine ophthalmic treatment regimen were in the range of nonquantifiable to 4.7 ng/mL with the majority of levels falling between 1.5 to 2.5 ng/mL. Maximum serum concentration following a single oral administration of a 250 mg ciprofloxacin tablet is about 1200 ng/mL.

INDICATIONS AND CLINICAL USE

NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) is indicated for the treatment of the following infections of the eye and its adnexae when caused by susceptible strains of the designated bacteria.

Corneal Ulcers: *Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae*

Conjunctivitis: *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus* (*Viridans* group)*, Streptococcus pneumoniae, Haemophilus influenzae*

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin, other quinolones, including nalidixic acid, or any other component of the medication.

WARNINGS

NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) IS NOT FOR INJECTION INTO THE EYE.

PRECAUTIONS

General

Prolonged use of NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones by systemic administration. 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 reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy and the patient monitored until the risk of anaphylaxis is no longer present. Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving systemically administered ciprofloxacin along with other drugs. One

report exists of anaphylaxis in a patient treated with topical ciprofloxacin concomitantly with several other antibiotics and medications. The possibility that these reactions were related to ciprofloxacin cannot be excluded. 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 29 (18.8%) out of 154 patients administered ciprofloxacin ophthalmic solution. The onset of the precipitate was within 24 hours to 7 days (solution) after starting therapy. In 16 patients administered ciprofloxacin ophthalmic solution, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24-72 hours), in four patients, resolution was noted in 10-13 days. In one patient, the precipitate was immediately irrigated out upon its appearance.

In six 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 two patients, outcome information was unavailable. The presence of the white precipitate did not preclude continued use of ciprofloxacin ophthalmic solution, nor did it adversely affect the clinical course of the ulcer or visual outcome. A literature report exists of a single case of ciprofloxacin-associated dense precipitate apparently interfering with re-epithelialization.

In patients with large (>4 mm) and/or deep stromal ulcers, the clinical success rate was lower for both ciprofloxacin and standard (fortified antibiotics) therapy.

Drug Interactions

Specific drug interaction studies have not been conducted with ciprofloxacin ophthalmic solution. 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 cyclosporin concomitantly.

Pregnancy

There are no adequate and well controlled studies of ciprofloxacin ophthalmic solution in pregnant women. This drug should be used in pregnant women only if in the physician's opinion, the benefit clearly outweighs any potential unknown risks.

Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human 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 in rabbits, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed.

Nursing Mothers

It is not known whether topically applied ciprofloxacin ophthalmic solution is excreted in human milk, however, it is known that orally administered ciprofloxacin is excreted in milk of lactating rats and that other drugs of this class are excreted in human milk. For this reason, and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of ciprofloxacin ophthalmic solution in children less than one year of age have not been demonstrated. Ciprofloxacin ophthalmic solution has been used to treat conjunctivitis in 123 children between the ages of one and twelve years and no serious adverse event was reported in these patients.

Ciprofloxacin and quinolone-related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. Topical ocular administration of ciprofloxacin to immature animals (Beagle dogs) did not cause arthropathy or demonstrate any articular lesions and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

In 634 children treated orally with ciprofloxacin, clinical and radiologic monitoring did not reveal any skeletal toxicity felt to be quinolone-related. However, there are a small number of reports of arthralgia in children, associated with oral ciprofloxacin therapy. This arthralgia has been shown to be reversible on discontinuation of the systemic medication.

ADVERSE REACTIONS

During clinical studies, treatment related adverse events to ciprofloxacin ophthalmic solution were mild, infrequent in occurrence and non-serious in nature, and did not lead to premature discontinuation of therapy. The most frequently reported adverse events that were considered related or possibly related to ciprofloxacin ophthalmic solution were: transient discomfort, i.e., stinging, burning, irritation (8.6%), noticeable taste (4.5%), foreign body sensation (1.8%), and itching (1.2%). Treatment-related or possibly related medical events occurring between 0.5 and 1% incidence were: lid margin crusting, crystals/scales, erythema/redness, dryness, discharge, corneal staining, keratopathy/keratitis, hyperemia/congestion and tearing.

In clinical trials in which 154 patients were treated for bacterial corneal ulcers, the most frequently reported adverse event related or possibly related to therapy was a white crystalline precipitate seen in 29 (18.8%) patients. The precipitate required no adjunctive therapy and resolved spontaneously with continued ciprofloxacin use.

Other rarely reported events related or possibly related to ciprofloxacin ophthalmic solution included: ocular congestion, photophobia, pain, vision decrease, chemosis, corneal infiltrate, inflammation, blurred vision, corneal toxicity, allergy, intolerance, lid edema, heavy sensation, swelling, conjunctival reaction, numbing sensation, conjunctivitis, punctate epithelial erosion, and worsened infiltrate and headache.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

A topical overdosage of ciprofloxacin ophthalmic solution is considered to be a remote possibility. Discontinue medication when heavy or protracted use is suspected. A topical overdosage may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION

Conjunctivitis

Adults and Children (above the age of 1 year):

Instill one or two drops of NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) into the conjunctival sac(s) every two hours while awake for two days and then two drops every four hours while awake for 5 days.

Corneal Ulcer

Adults and Children (above the age of 12 years):

Instill two drops of NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) 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. If corneal re-epithelialization has not occurred after 14 days, the continuation of the dosing regimen is at the discretion of the attending physician.

Special Instructions

Patients should be advised to avoid contamination of the dispensing tip.

PHARMACEUTICAL INFORMATION

Drug Substance

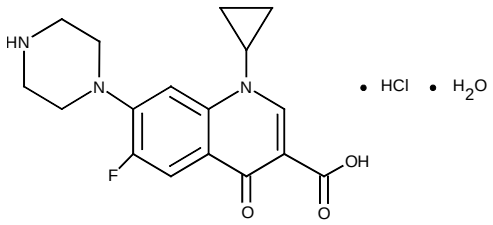
Proper Name: Ciprofloxacin Hydrochloride

Chemical Name(s):

1) 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride, monohydrate;

2) 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate.

Structural Formula:



Molecular Formula: $C_{17}H_{18}FN_3O_3.HCl.H_2O$

Molecular Weight: 385.82

Description: Ciprofloxacin hydrochloride is a faintly yellowish to light yellow crystalline powder with a melting point of 306°C. It is sparingly soluble in water and the pH of a 2.5% solution is between 3.0 and 4.5.

Composition

Each mL of NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) contains ciprofloxacin hydrochloride monohydrate 3.5 mg equivalent to 3 mg base, with the following inactive ingredients: Benzalkonium chloride 0.006% as preservative, edetate disodium, acetic acid, mannitol, sodium acetate, hydrochloric acid and/or sodium hydroxide (to adjust pH) and water for injection.

Stability And Storage Recommendations

Store at 15-30°C (59-86°F) in well-closed containers. Protect from light. Use within 28 days after opening container.

AVAILABILITY OF DOSAGE FORMS

NU-CIPROFLOX(Ciprofloxacin Ophthalmic Solution USP) is supplied as a sterile ophthalmic solution in white translucent plastic bottles containing 5 mL (partially filled into an 11 mL bottle) and 10 mL (filled to capacity).

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against both gram-positive and gram-negative organisms. The bactericidal action of ciprofloxacin results from interference of the enzyme, DNA gyrase, needed for the synthesis of bacterial DNA. The *in vitro* activity of ciprofloxacin against various strains of microorganisms is listed in Table 1.

The minimum bactericidal concentration (MBC) generally does not exceed the minimum inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed.

Table 1
MIC_{90}S for Potential Ocular Pathogens

	# Strains	MIC_{90} (µg/mL)	MIC Range (µg/mL)
A. Gram-Positive Aerobic Bacteria			
Staphylococcus aureus	397	0.5	0.25 – 4.0
Staphylococcus aureus (methicillin-susceptible)	287	0.5	0.5
S. aureus (methicillin-resistant)	339	0.25	0.25 – 4.0
S. epidermidis	136	0.25	0.25 – 2.0
Staphylococcus, other coagulase-negative	432	0.25	0.25 – 1.0
Streptococcus pneumoniae	331	1.0	1.0 – 2.0
S. pyrogenes	215	0.25	0.25 – 2.0
Streptococcus, Viridans group	87	2.0	2.0 – 4.0
Enterococcus spp	580	0.06	0.06 – 8.0
Corynebacterium spp including JKs	52	0.5	0.5 – 1.0
B. Gram Negative Aerobic Bacteria			
Neisseria gonorrhoeae	335	0.004	≤ 0.002 – 0.06
N. meningitides	215	≤ 0.06	0.008 – 0.06
Haemophilus influenzae	717	≤ 0.06	0.00 – 0.03
Moraxella (branhamella) catarrhalis	246	≤ 0.06	0.015 – 0.5
Acinetobacter spp	279	1.0	0.5 – 2.0
Pseudomonas aeruginosa	801	≤ 1.0	0.012 – 1.0
Ps. Aeruginosa (gentamicin-resistant)	11	4.0	4.0
Escherichia coli	634	≤0.25	≤ 0.004 – 0.25
Klebsiella pneumoniae	376	0.125	0.015 – 0.5
Proteus mirabilis	464	0.125	0.015 – 0.25
Serratia marcescens	238	1.0	0.125 – 0.8
C. Anaerobes			
Bacteroides spp	365	16.0	0.015 - 2.0
Clostridium spp (not C. difficile)	156	8.0	0.5 – 32.0
Peptostreptococcus spp	30	4.0	2.0 – 4.0
D. Chlamydia spp.	68	2.0	1.0 – 2.0

Cross-resistance with other quinolones has been observed. However, organisms resistant to antimicrobial agents

having other mechanisms of action (e.g., beta-lactam and aminoglycoside antibiotics) may be sensitive to ciprofloxacin. Conversely, organisms resistant to ciprofloxacin might be sensitive to antimicrobial agents having other mechanisms of action.

PHARMACOLOGY

Animal Pharmacology

After topical application of ciprofloxacin 0.3% (1 drop every 30 minutes for a total of 6 doses), the concentration of ciprofloxacin achieved in the aqueous humor of rabbits when the corneal epithelium was intact, was 4.8 μg/mL and when debrided was 12.9 μg/mL.

Human Pharmacology

Topically applied ciprofloxacin ophthalmic solution 0.3% w/v is absorbed systemically with ciprofloxacin plasma concentrations approaching steady state at the end of dosing each day. Ciprofloxacin plasma concentrations following a routine ophthalmic treatment regimen were in the range of nonquantifiable to 4.7 ng/mL with the majority of levels falling between 1.5 to 2.5 ng/mL. Maximum serum concentration following a single oral administration of a 250 mg ciprofloxacin tablet is about 1200 ng/mL.

TOXICOLOGY

Ciprofloxacin has been shown to cause arthropathy in immature animals of most species tested following oral administration. However, in a one-month topical ocular study, 0.3% or 0.75% ciprofloxacin ophthalmic solution administered four times per day to immature Beagle dogs did not demonstrate any articular lesions. Based on ocular toxicology studies performed in rabbits, the ocular effects produced by an exaggerated topical ocular exposure to 0.3%, 0.75% or 1.5% ciprofloxacin ophthalmic solution were minimal and transient in nature, confined to the conjunctiva and generally comparable to those effects observed in the untreated control and vehicle control groups. In a subchronic, one-month topical ocular irritation study, 0.3% to 1.5% ciprofloxacin ophthalmic solution did not demonstrate a cumulative ocular irritation potential and did not demonstrate any apparent systemic or ocular toxicity in rabbits.

The cataractogenic potential of oral ciprofloxacin in rats was evaluated. The results indicate that ciprofloxacin was not co-cataractogenic. An intravenous study of ciprofloxacin at levels up to 20 mg/kg over a six month period in Rhesus monkeys indicated that there were no signs of changes in lens transparency due to the administration of ciprofloxacin.

Mutagenesis

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 2 of the 8 tests were positive but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Carcinogenesis

Long term carcinogenicity studies in mice and rats have been completed. After oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

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