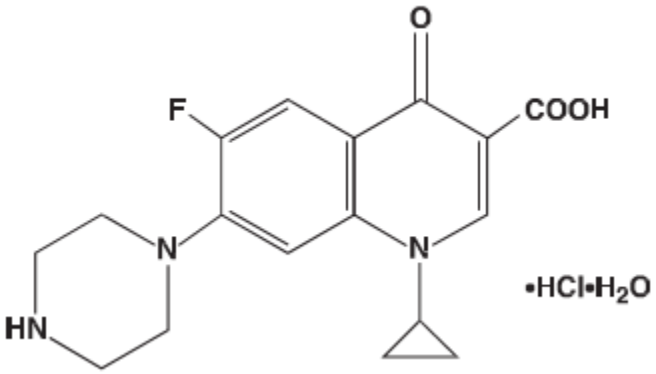
CIPROFLOXACIN hydrochloride

CILOXAN®
3 mg/mL (0.3%)
Sterile Ophthalmic Solution
Antibacterial

DESCRIPTION :
Ciprofloxacin HCl 0.3% (CILOXAN®) 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 C17H18FN3O3•HCl•H2O 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.

1 mL of CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution contains 3.5 mg ciprofloxacin hydrochloride equivalent to 3 mg base.
Excipients: Inactive ingredients are disodium edetate 0.05%, mannitol 4.6%, glacial acetic acid, sodium acetate, hydrochloric acid and/or sodium hydroxide for pH adjustment, and purified water.
The pH is approximately 4.5 and the osmolality is approximately 300 mOsm.
Preservative: Benzalkonium chloride 0.006% (0.06 mg/ mL)

CLINICAL PHARMACOLOGY :
Systemic Absorption: A systemic absorption study was performed in which CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile 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).

Gram-Positive :
Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains)
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 CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile 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 (CILOXAN®) 3 mg/mL (0.3%) Sterile 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*	Conjunctivitis :	*Haemophilus influenzae*
	*Serratia marcescens**		*Staphylococcus aureus*
	Staphylococcus aureus		*Staphylococcus epidermidis*
	Staphylococcus epidermidis		*Streptococcus pneumoniae*
	Streptococcus pneumoniae		
	*Streptococcus (Viridans Group)**		

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

CONTRAINDICATIONS :

Hypersensitivity to the active substance, to other quinolones, or to any of the excipients.

WARNINGS :

FOR EXTERNAL USE ONLY - NOT FOR INJECTION INTO THE EYE. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systemically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment with epinephrine and other resuscitation measures, including intravenous fluids, intravenous antihistamines, corticosteroids, and pressor amines. Oxygen and airway management should be administered where clinically indicated. Remove contact lenses before using.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Therefore treatment with CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution should be discontinued at the first sign of tendon inflammation.

PRECAUTIONS :

General: As with all antibacterial preparation, prolonged use may lead to overgrowth of non-susceptible bacterial strains or 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).

Contact lens wear is not recommended during treatment of an ocular infection. Therefore, patients should be advised not to wear contact lenses during treatment with CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution.

CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution and wait at least 15 minutes before reinsertion.

Information for Patients :
Do not touch dropper tip to any surface as this may contaminate the solution.

Interaction with other medicinal products and other forms of interaction:
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.

Given the low systemic concentration of Ciprofloxacin following topical ocular administration of the product, drug interactions are unlikely to occur.

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 Miotic 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.

Studies have not been performed in humans to evaluate the effect of topical administration of Ciprofloxacin on fertility. Oral administration in animals does not indicate direct harmful effects with respect to fertility.

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 embryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women.

There are no or limited amount of data from the use of CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution in pregnant women. Animal studies with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity. CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding:
Ciprofloxacin is excreted in human milk after its oral administration. It is unknown whether ciprofloxacin is excreted to human milk following topical ocular administration. A risk to the suckling child cannot be excluded. Caution should be exercised when CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution is administered to a nursing mother.

UNDESIRABLE EFFECTS:
The following adverse reactions have been reported during clinical trials with CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution and are classified according to the subsequent convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

The following undesirable effects were reported in association with the ophthalmic use CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution:

System Organ Classification	**Adverse reactions** *MedDRA Preferred Term (v. 15.1)*
Immune system disorders	*Rare:* hypersensitivity
Nervous system disorders	*Uncommon*: headache *Rare:* dizziness
Eye disorders	*Common:* corneal deposits, ocular discomfort, ocular

	hyperaemia *Uncommon*: keratopathy, punctate keratitis, corneal infiltrates, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, dry eye, eye swelling, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting, eyelid exfoliation, conjunctival oedema, erythema of eyelid *Rare:* ocular toxicity, keratitis, conjunctivitis, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, hordeolum, eye irritation, eye inflammation
Ear and labyrinth disorders	*Rare:* ear pain
Respiratory, thoracic and mediastinal disorders	*Rare:* paranasal sinus hypersecretion, rhinitis
Gastrointestinal disorders	*Common:* dysgeusia *Uncommon:* nausea *Rare:* diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	*Rare:* dermatitis

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	**Adverse reactions** *MedDRA Preferred Term (v. 15.1)*
Musculoskeletal and connective tissue disorders	tendon disorder

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon administration, the patient must wait until the vision clears before driving or using machinery.

OVERDOSAGE:
Due to the characteristics of this preparation no toxic effects are to be expected with an ocular overdose of this product, nor in the event of accidental ingestion of the contents of one bottle/tube. A topical overdose of CIPROFLOXACIN hydrochloride (CILOXAN®) 3 mg/mL (0.3%) Sterile Ophthalmic Solution may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION:
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, instiIl 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.

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.

AVAILABILITY:
As a sterile ophthalmic solution: 5 mL in plastic DROPTAINER® dispenser.

STORAGE:
Store at temperatures not exceeding 30°C. Do not refrigerate or freeze. Protect from light. Keep out of reach of children.
Discard one month after opening.

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.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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