

CILOXAN[®] (ciprofloxacin hydrochloride) 3mg/g Eye Ointment

NAME OF MEDICINE

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PRESENTATION

CILOXAN Eye Ointment contains the equivalent of 3 mg/g ciprofloxacin base, and have been formulated as a sterile, multiple-dose product, for topical ophthalmic use.

CILOXAN Eye Ointment also contains mineral oil and white petrolatum.

USES

Actions

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms, possessing the greatest antibacterial activity of all quinolones.

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):

Gram-Positive:

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains)

Staphylococcus epidermidis

Streptococcus pneumoniae

Viridans group of *Streptococcus*

Gram-Negative:

Pseudomonas aeruginosa

Serratia marcescens

Haemophilus influenzae

Other Organisms:

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). A plasmid-mediated bacterial resistance does not appear to occur with the fluoroquinolone class of antibiotics, however, parallel resistance is seen with this group of gyrase inhibitors.

Due to its special mode of action there is no cross-over resistance between ciprofloxacin and other antibacterial compounds with different chemical structures, such as β -lactam antibiotics, aminoglycosides, tetracyclines, macrolide and peptide antibiotics as well as sulfonamides, trimethoprim and nitrofurantoin derivatives.

Pharmacokinetics

Absorption studies in humans with the CILOXAN Eye Ointment have not been conducted.

Two systemic absorption studies were performed in which CILOXAN Eye Drops using the conjunctivitis or corneal ulcer dosing regimen. In the study involving the more intensive dosing regimen (ie corneal ulcer indication), two drops were administered in one eye every 15 minutes for six hours, every 30 minutes for 18 hours, then two drops hourly for one day , followed by two drops every 4 hours for 5 additional days.

In each study, the maximum reported plasma concentration of ciprofloxacin was less than 5 ng/mL (some 450-fold less than levels observed following simple 250 mg oral administration). The mean concentration in each of the studies were less than 2.5 ng/mL.

Toxicological Properties

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 with ciprofloxacin ophthalmic solution in immature Beagle dogs did not demonstrate any articular lesions.

Acute topical ocular toxicology studies performed in rabbits employing an exaggerated topical ocular exposure to 0.3%, 0.75%, or 1.5% ciprofloxacin ophthalmic solution showed findings that 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.

A subchronic, one-month topical ocular irritation study of 0.3% to 1.5% ciprofloxacin ophthalmic solution did not demonstrate any apparent systemic or ocular toxicity in rabbits.

Clinical Studies

The data generated in seven multicentre, controlled, clinical studies demonstrate that ciprofloxacin is effective, both microbiologically and clinically, in the treatment of corneal ulcers, conjunctivitis, and blepharitis of bacterial aetiology. Ciprofloxacin was found to be effective (at $\leq 2 \mu\text{m/mL}$) against all the major groups of organisms associated with the above ocular diseases. Of special note is the clinical success rate of 93% against *Pseudomonas aeruginosa* associated with corneal ulcers. Ciprofloxacin was effective in eradicating infective bacteria associated with conjunctivitis in adults, and in children. Ciprofloxacin also eradicated or reduced the bacteria in the eyes of 97.6% of blepharitis patients compared with 11.8% of patients on placebo.

INDICATIONS

Treatment of corneal ulcers, conjunctivitis and blepharitis caused by susceptible strains of bacteria in adults and children 12 months of age or older.

DOSAGE AND ADMINISTRATION

Corneal Ulcers

The recommended dosage regimen for the treatment of **corneal ulcers** is: 1.25 cm ribbon applied into the conjunctival sac every 1-2 hours around the clock for two days, then every 4 hours for a further 12 days. The dosing may be extended at the discretion of the physician.

Bacterial Conjunctivitis/Blepharitis

The recommended dosage regimen for the treatment of **bacterial conjunctivitis** is: 1.25 cm ribbon applied into the conjunctival sac (or on the lid margin) three times daily for two days, then twice daily for a further five days. The dosing may be extended at the discretion of the physician.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

FOR TOPICAL USE ONLY - NOT FOR INJECTION

FOR OCULAR USE ONLY

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 oedema, dyspnoea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with adrenaline and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Moderate to severe phototoxicity manifested by an exaggerated sunburn reaction has been observed in some patients who were exposed to direct sunlight while receiving some members of the quinolone class of drugs, including oral ciprofloxacin. Excessive sunlight should be avoided.

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. When using CILOXAN eye ointment one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Whenever clinical judgment dictates, the patient's eye(s) 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.

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 CILOXAN 0.3% Eye Ointment should be discontinued at the first sign of tendon inflammation.

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 CILOXAN eye ointment.

Use in Pregnancy-Category B3

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 foetus 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. As a precautionary measure, it is preferable to avoid the use of CILOXAN during pregnancy. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

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 is administered to a nursing mother.

Use in Children

Safety and effectiveness of CILOXAN Eye Ointment were determined in 192 children between the ages of one to 12 years. No serious adverse event was reported in these patients. These clinical studies have indicated that dosage modifications are not required for children. There is no experience in children less than 1 year old.

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.

Use of CILOXAN eye ointment in neonates with ophthalmia neonatorum is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition.

Use in Elderly

Clinical studies have indicated dosage modifications are not required for the elderly

Use in Hepatic and Renal Impairment

No studies have been performed using CILOXAN Eye Ointment in patients with kidney or liver problems.

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)

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively) and rats (oral doses up to 241 mg/kg/day and 328 mg/kg/day in males and females, respectively) showed no evidence of carcinogenicity.

Other Animal Studies

Special studies included a cataractogenic potential study of systemic ciprofloxacin in rats. The results indicated that ciprofloxacin was not co-cataractogenic. An intravenous study of ciprofloxacin at dose levels up to 20 mg/kg over a 6-month period in Rhesus monkeys

indicated there were no signs of changes in lens transparency due to the administration of ciprofloxacin.

The arthropathogenic potential of some quinolones in immature animals after oral administration is recognised. 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.

Effects on Ability to Drive and Use Machines

Temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

ADVERSE EFFECTS

The most frequently reported drug related adverse reaction was local discomfort (transient stinging and burning upon application) (1.4%). In corneal ulcer studies with frequent administration of the drug, white precipitates were seen in approximately 3% of patients. The precipitates resolved after continuous application of CILOXAN Eye Ointment. The precipitate does not preclude continued use of CILOXAN Eye Ointment nor does it adversely affect the clinical course of the recovery process.

Uncommon ophthalmic events (occurring in less than 1% and greater than 0.1% of patients) included blurred vision (0.8%), hyperaemia (0.7%), pruritus (0.6%), pain (0.6%), vision decrease (0.6%), tearing (0.4%) and photophobia (0.3%).

Uncommon systemic events (occurring in less than 1% and greater than 0.1% of patients) included taste perversion (metallic taste)(0.5%) and dermatitis (0.2%).

Post-marketing Experience

The following adverse reactions are classified according to the following convention: very common, common, uncommon, rare, very rare, or not known (cannot be estimated from the available data), according to system organ classes. Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience.

Infections and infestations

Rare (> 0.01% to ≤ 0.1%): hordeolum, rhinitis

Immune system disorders

Rare (> 0.01% to ≤ 0.1%): hypersensitivity

Nervous system disorders:

Common (> 1% to < 10%): dysgeusia

Uncommon (> 0.1% to ≤ 1%): headache

Rare (> 0.01% to ≤ 0.1%): dizziness

Eye disorders

Common (> 1% to < 10%): corneal deposits, ocular discomfort, ocular hyperaemia

Uncommon (> 0.1% to ≤ 1%): keratopathy, corneal infiltrates, corneal staining, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, dry eye, eye

swelling, eye pruritus, foreign body sensation in eyes, lacrimation increased, eye discharge, eyelid margin crusting, eyelid exfoliation, conjunctival oedema, erythema of eyelid
Rare (> 0.01% to ≤ 0.1%): ocular toxicity, punctate keratitis, keratitis, conjunctivitis, corneal disorder, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, eye irritation, eye inflammation, conjunctival hyperaemia

Ear and labyrinth disorders

Rare (> 0.01% to ≤ 0.1%): ear pain

Respiratory, thoracic and mediastinal disorders:

Rare (> 0.01% to ≤ 0.1%): paranasal sinus hypersecretion

Gastrointestinal disorders:

Uncommon (> 0.1% to ≤ 1%): nausea

Rare (> 0.01% to ≤ 0.1%): diarrhoea, abdominal pain

Skin and subcutaneous tissue disorders:

Rare (> 0.01% to ≤ 0.1%): dermatitis

General disorders and administration site conditions:

Rare (> 0.01% to ≤ 0.1%): drug intolerance

Investigations

Rare (> 0.01% to ≤ 0.1%): laboratory test abnormal

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

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 oedema, dyspnoea, urticaria, and itching.

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including the Achilles tendon. To date, clinical and post marketing data have not demonstrated a clear association between CILOXAN and musculoskeletal and connective tissue adverse reactions.

In patients with corneal ulcer and frequent administration of CILOXAN, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of CILOXAN. The precipitate does not preclude the continued use of CILOXAN, nor does it adversely affect the clinical course of the recovery process.

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 have been associated with transient elevations in serum creatinine in patients receiving cyclosporin concomitantly.

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

OVERDOSAGE

A topical overdose of CILOXAN Eye Ointment may be flushed from the eye(s) with warm tap water. Accidental oral ingestion of CILOXAN is not likely to be associated with toxicity. Treatment of any exposure is symptomatic and supportive.

PHARMACEUTICAL PRECAUTIONS

Store below 25°C. Do not freeze. Discard container 4 weeks after opening. Consumer Product Information is supplied with this product.

Incompatibilities

Not applicable.

MEDICINE CLASSIFICATION

Prescription Only Medicine.

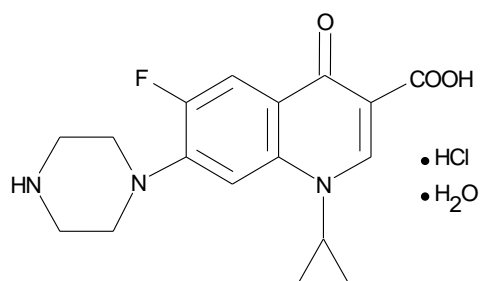
PACKAGE QUANTITIES

Eye ointment tube containing 3.5 g of sterile eye ointment.

FURTHER INFORMATION

Pharmaceutical

Ciprofloxacin, a faint to light yellow crystalline powder which is soluble in water, is a fluoroquinolone antibacterial. The chemical structure of ciprofloxacin hydrochloride is represented as:



Empirical formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular weight: 385.8

Chemical name: The monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

CAS Number: 86393-32-0

SPONSOR DETAILS

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