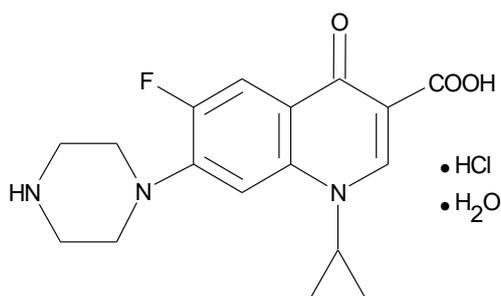


## PRODUCT INFORMATION

### CILOXAN\* (ciprofloxacin) Eye Drops 0.3%

#### NAME OF THE MEDICINE

CILOXAN Eye Drops contain ciprofloxacin hydrochloride. 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 Registry Number: 86393-32-0.

#### DESCRIPTION

CILOXAN Eye Drops contain the equivalent of 3 mg/mL ciprofloxacin base, and have been formulated as a sterile, multiple-dose product, for topical ophthalmic use. The pH of CILOXAN Eye Drops is approximately 4.5 and the osmolality is approximately 300 mOsm.

Ciprofloxacin, a faint to light yellow crystalline powder which is soluble in water, is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens.

CILOXAN Eye Drops also contain sodium acetate, acetic acid, mannitol, disodium edetate, hydrochloric acid and/or sodium hydroxide (to adjust pH), purified water and benzalkonium chloride (0.06 mg/mL) as preservative.

## PHARMACOLOGY

### Systemic Absorption

A systemic absorption study was performed in which CILOXAN Eye Drops were 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):

#### 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).

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 TRIALS**

Following therapy with CILOXAN Eye Drops 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 multicentre 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**

Treatment of bacterial keratitis (infected corneal ulcers) and severe bacterial conjunctivitis caused by organisms susceptible to ciprofloxacin in adults and children 12 months of age or older.

## **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, including nalidixic acid, may also contraindicate the use of ciprofloxacin.

## **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 drops 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 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 Drops should be discontinued at the first sign of tendon inflammation.

CILOXAN eye drops contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. 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 drops.

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 EFFECTS).

### **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 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 embryo-toxicity 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 fetus.

### **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.

### **Paediatric Use**

Safety and effectiveness in children below the age of 1 year particularly in neonates is very limited and 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.

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

## **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.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin on 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<sub>79</sub> 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.

## **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.

## **INTERACTIONS WITH OTHER MEDICINES**

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.

## ADVERSE EFFECTS

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).

Tabulated adverse reaction data (considered to be related or possible related to treatment), providing comparisons to placebo and other active comparators (to an incidence of 1% or greater in the CILOXAN Eye Drops 0.3% treatment group), which have been generated from all adult clinical studies with CILOXAN Eye Drops 0.3% are provided below:

<b>Tabulated Adverse Reaction Data Comparing Incidence (%) Figures</b>			
<b>Adverse Reaction</b>	<b>CILOXAN Eye Drops 0.3% (n = 950)</b>	<b>Tobramycin 0.3% (n = 530)</b>	<b>Placebo (n = 202)</b>
<b>Ocular</b>			
Discomfort	9.7	2.2	7.9
White precipitate	3.6	-	-
Foreign body sensation	2.0	-	-
Hyperaemia/erythema/redness	1.2	1.9	1.4
Itching	1.1	-	1.9
<b>Special Senses</b>			
Taste abnormality	5.0	-	-

"-" Incidence less than 1%.

Uncommon ophthalmic events (occurring in less than 1% and greater than 0.1% of patients) included lid margin crusting, crystals/scales, dryness/dry eye, discharge, corneal staining, keratopathy/keratitis, tearing, photophobia, pain, vision decrease, chemosis, corneal infiltrates, inflammation, blurred vision, corneal toxicity, allergy, intolerance, lid oedema, heavy sensation, swelling, conjunctival reaction, numbing sensation, conjunctivitis, punctate epithelial erosion and progression of infiltrate.

Uncommon systemic events (occurring in less than 1% and greater than 0.1% of patients) included nausea and sinus drainage.

### **Post-marketing Events**

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

Additional adverse reactions identified from post-marketing surveillance include the following.

Frequencies cannot be estimated from the available data.

### ***Musculoskeletal and connective tissue disorders***

Tendon disorder

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.

The incidence of adverse events to marketed drugs such as CILOXAN Eye Drops is difficult to reliably assess due to the nature of spontaneous, voluntary reporting systems and the problems associated with estimating the total exposure to the drug. Post-marketing data must also be evaluated in the knowledge that causality may be difficult or impossible to establish.

The most common adverse events reported in the Post-marketing period for CILOXAN Eye Drops 0.3% were precipitate in the eye, eye discomfort, non-specific ocular irritation and foreign body sensation. No adverse events were reported at an incidence greater than 1:100,000

## **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, instil 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 drop instilled into the conjunctival sac(s) every two hours while awake for two days and one drop every four hours while awake for the next five days.

## **OVERDOSAGE**

A topical overdose of CILOXAN Eye Drops 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.

## **POISONS SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (Schedule 4)

## **PRESENTATION AND STORAGE CONDITIONS**

As a sterile ophthalmic solution 2.5 and 5 mL in plastic DROP-TAINER\* dispensers.

Store below 25°C. Do not refrigerate or freeze. Protect from light.

Discard container 4 weeks after opening.

*Consumer Product Information is included with this product.*

## **NAME AND ADDRESS OF SPONSOR**

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

Approved by TGA on 26 November 1993

## **DATE OF MOST RECENT AMENDMENT**

26 July 2017

\*a trademark of Novartis

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