# CILOXAN®

**Sterile Ophthalmic and Otic Solution**
**(Ciprofloxacin 0.3 %)**

## 1 Tradename(s)

CILOXAN® Sterile Ophthalmic and Otic Solution 0.3%.
CILOXAN (ciprofloxacin hydrochloride solution), 0.3% as base

## 2 Description and composition

Eye/Ear drops, solution.

**Active substance(s)**

1 ml of solution contains 3.5 mg ciprofloxacin hydrochloride monohydrate equivalent to 3 mg ciprofloxacin base.

**Excipients**

Excipient with known effect: 1 mL of solution contains 0.06 mg of benzalkonium chloride.

Other excipients: disodium edetate, mannitol, acetic acid, sodium acetate trihydrate, hydrochloric acid and / or sodium hydroxide for pH adjustment, and purified water.

## 3 Indications

**Ocular use:**

- Ciloxan Eye drops is indicated for the treatment of corneal ulcers and superficial infections of the eye and its adnexa, caused by strains presumed or reported susceptible to Ciprofloxacin, in particular *Pseudomonas aeruginosa* and other Gram-negative bacteria resistant to usual treatments.

**Otic use:**

- Ciloxan Ear drops is indicated for localized or diffuse otitis externa accompanied by a strong inflammatory reaction and of which the strains are susceptible to Ciprofloxacin.

## 4 Dosage regimen and administration

### Eye drops

**Dosage regimen**

**Corneal ulcers**
Ciloxan Eye drops must be administered at the following intervals, even during night-time:

- On the first day, instill 2 drops into the affected eye(s) every 15 minutes for the first 6 hours and then 2 drops into the affected eye(s) every 30 minutes for the remainder of the day.
- On the second day, instill 2 drops into the affected eye(s) hourly.

- On the third through the fourteenth day, place two drops into the affected eye(s) every 4 hours. If the patient needs to be treated longer than 14 days, the dosing regimen is at the discretion of the attending physician.

**Superficial bacterial infections of the eye and adnexa**

- For the first two days instill one or two drops into the conjunctival sac of the infected eye(s) every two hours during daytime.
- Then one or two drops every four hours during daytime until the bacterial infection is resolved.

**Special populations**

**Renal and hepatic impairment**

No studies have been performed in patients with renal or hepatic impairment.

**Pediatric patients**

Safety and efficacy in pediatric patients below age of 1 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 ophthalmic dosage form has any effect on the weight bearing joints.

## Ear drops

**Dosage regimen**

First thoroughly clean the external auditory duct. It is more agreeable to administer the solution at room temperature, and better still at body temperature, because in this way vestibular stimulation is avoided. Apply the product dropwise in the external ear duct; the dosage is 3 to 4 drops, 2 to 4 times per day, or more frequently, if required. The patient should first lie on the opposite side in relation to the infection and should preferably remain lying in this position for 5 to 10 minutes. After local cleaning, an impregnated tent of gauze or a hydrophylic plug of cotton can also be inserted in the ear duct, and is generally left in place for 1 to 2 days, but should be impregnated to saturation with the product 2 times per day. In general, the duration of the treatment does not exceed 5 to 10 days. In some cases, the treatment can be prolonged, but, in such cases, it is advisable that the sensitivity of the local flora be demonstrated. As with all antibacterial preparations, prolonged use may lead to overgrowth with non-susceptible microorganisms or fungi.

**Special populations**

**Renal and hepatic impairment**

No studies have been performed in patients with renal or hepatic impairment.

**Pediatric patients**

Safety and efficacy in pediatric patients below age of 1 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 ophthalmic dosage form has any effect on the weight bearing joints.

**Method of administration**

**Ciloxan Eye drops**

- For ocular use only.

- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- To avoid contamination, the tip of the dropper / tube should not touch any surface and should also not come into contact with the eye as this may cause injury to the eye.
- Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.
- Patients should be advised not to wear contact lenses during treatment with CILOXAN Eye/Ear drops solution. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of CILOXAN Eye/Ear drops solution and wait at least 15 minutes before reinsertion.
- If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointment should be administered last.

**Ciloxan Ear drops**

- For otic use only.
- To avoid contamination, the dropper tip should not touch the ear or any other surface.
- The solution should be warmed by holding the bottle in the hand for a few minutes to avoid any unpleasant sensation which may result from the instillation of a cold suspension.

## 5 Contraindications

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

## 6 Warnings and precautions

**Ocular and otic use**

- 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. Ciloxan should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction. Serious acute hypersensitivity reactions to Ciloxan may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.
- As with all antibacterial preparations, prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.
- 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 Eye/Ear drops solution should be discontinued at the first sign of tendon inflammation.

**Ocular use**

- For ocular use only.
- In patients with corneal ulcer and frequent administration of Ciloxan Eye Drops, white topical ocular precipitates have been observed which resolved after continued application of Ciloxan Eye drops. The precipitate does not preclude the continued use of Ciloxan Eye drops, nor does it interfere with antibacterial therapeutic response. However, precipitates may delay epithelial healing.
- Contact lens wear is not recommended during treatment of an ocular infection.

**Special excipients**

- Ciloxan Eye drops contains benzalkonium chloride which may cause eye irritation and may possibly discolor 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 CILOXAN Eye drops solution and wait at least 15 minutes before reinsertion.

**Otic use**

- For otic use only.
- Ciloxan Ear drops contains benzalkonium chloride which may be irritant and may cause skin reactions.

**Effects on ability to drive and use machines**

Ocular use:
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.

Otic use:
There are no data on the effect of CILOXAN Eye/Ear drops solution on the ability to drive and use machine.

## 7 Adverse drug reactions

**Ocular use**

**Tabulated summary of adverse drug reactions from clinical trials**

Adverse reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

**Table 7-1 Frequency of adverse drug reactions in clinical trials – ocular use**

| System Organ Class | Adverse drug reactions |
|---|---|
| Nervous system disorders | *Uncommon:* headache<br>*Rare*: dizziness |
| Eye disorders | *Common*: corneal deposits, ocular hyperaemia, ocular discomfort<br>*Uncommon*: keratopathy, punctate keratitis, corneal infiltrates, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, eye swelling, eye pruritus, eyelid exfoliation, conjunctival oedema, erythema of eyelid, dry eye, lacrimation increased, eye discharge, eyelid margin crusting<br>*Rare*: ocular toxicity, keratitis, corneal epithelium defect, hypoaesthesia eye, diplopia, conjunctivitis, hordeolum, asthenopia, 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*<br>*Uncommon: nausea*<br>*Rare: diarrhoea, abdominal pain* |
| Skin and subcutaneous tissue disorders | *Rare*: dermatitis |
| Immune system disorders | *Rare:* hypersensitivity |

**Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following adverse drug reactions have been derived from post-marketing experience with Ciloxan Eye drops via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known) – ocular use**

| System Organ class | Adverse drug reactions |
|---|---|
| Musculoskeletal and connective tissue disorders | Tendon disorder |

**Otic use**

**Tabulated summary of adverse drug reactions from clinical trials**

Adverse drug reactions from clinical trials (Table 7-3) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

**Table 7-3 Frequency of adverse drug reactions in clinical trials – otic use**

| System Organ Class | Adverse drug reactions |
|---|---|
| Nervous system disorders | *Uncommon:* headache |
| Ear and labyrinth disorders | *Uncommon:* otorrhoea,ear pain, ear congestion, ear pruritus |
| Skin and subcutaneous tissue disorders | *Uncommon*: dermatitis |
| General disorders and administration site conditions | *Uncommon*: pyrexia |

**Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following adverse drug reactions have been derived from post-marketing experience with Ciloxan Ear drops, solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 7-4 Adverse drug reactions from spontaneous reports and literature (frequency not known) – otic use**

| System Organ Class | Adverse drug reactions |
|---|---|
| Ear and labyrinth disorders | Tinnitus |

# 8 Interactions

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

# 9 Pregnancy, lactation, females and males of reproductive potential

## 9.1 Pregnancy

**Risk summary**

There are no adequate and well-controlled studies with Ciloxan in pregnant women to inform a product-associated risk.

Animal studies with Ciloxan do not indicate direct harmful effects with respect to reproductive toxicity. Ciprofloxacin was not teratogenic in mice and rats.

Ciloxan should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

## 9.2 Lactation

**Risk summary**

It is not known if ciprofloxacin is transferred into human milk following topical ocular or otic administration.

Systemically administered ciprofloxacin has been found in human milk.

However, a risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## 9.3 Females and males of reproductive potential

**Infertility**

There are no data regarding the effects of topical ocular or otic administration of Ciloxan on human fertility. Oral administration in animals does not indicate direct harmful effects with respect to fertility.

## 10 Overdosage

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular / otic overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

## 11 Clinical pharmacology

### Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: anti-infectives; Other anti-infectives.
ATC code: S03AA07

### Mechanism of action (MOA)

Ciloxan contains the fluoroquinolone ciprofloxacin. The cidal and inhibitory activity of ciprofloxacin involves inhibition of the α-subunit of bacterial enzyme, DNA gyrase (topoisomerase II) involved in gyrase-mediated DNA supercoiling and DNA synthesis. This process ultimately results in cell death. By targeting DNA gyrase, ciprofloxacin arrests bacterial cell growth and division by stabilizing the DNA-enzyme complex, which temporarily results in bacteriostasis. Subsequently, bacteria attempt but are unable to repair the DNA lesion. DNA ends from the ciprofloxacin-gyrase-DNA complex are eventually liberated creating lethal double-strand DNA breaks. Therefore, ciprofloxacin is bactericidal as well as bacteriostatic. The bactericidal activity of ciprofloxacin and other fluoroquinolones is concentration-dependent. Higher “kill rates” are achieved at peak concentrations. Ciprofloxacin has a very high in vitro activity against almost all Gram-negative microorganisms including Pseudomonas aeruginosa. It is also effective against Gram-positive bacteria, such as Staphylococci and Streptococci. Anaerobes are in general less susceptible.

### Mechanism of resistance

*In vitro* resistance to the antibacterial agent ciprofloxacin can be acquired through a stepwise process by target site mutation in both DNA gyrase and topoisomerase IV. The degree of cross resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance of efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

### Breakpoints

Currently, minimal inhibitory concentration (MIC) breakpoints as established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) take into consideration drug concentrations achievable systemically following oral or intravenous administration of the antibiotic. These Susceptible/Resistant (S/R in mg/L) breakpoints are used in every day clinical laboratory practice to predict clinical efficacy. However, when ciprofloxacin is used by topical administration as in the otic or ophthalmic administration, higher concentrations could be achieved, and the drug activity influenced by the physiochemical characteristics at this site of administration. There are no pharmacological data correlated with clinical outcome for

ciprofloxacin administered as a topical agent. As a result, the EUCAST suggests the following epidemiological cut-off values (ECOFF mg/L) derived from MIC distribution curves to indicate susceptibility to topical ciprofloxacin.

**EUCAST Recommended ECOFF Values for ciprofloxacin**

| **Micro-organisms** | **ECOFF (mg/L)** |
|---|---|
| *Staphylococcus* species | 1 mg/L |
| *Streptococcus pneumoniae* | 2 mg/L |
| *Haemophilus influenzae* | 0.06 mg/L |
| *Moraxella catarrhalis* | 0.12 mg/L |
| *Pseudomonas aeruginosa* | 0.5 mg/L |

While EUCAST antibiotic breakpoints are not considered applicable for correlation to topically applied antibiotics, the following EUCAST breakpoints for ciprofloxacin are consistent for general use.

**EUCAST S/R Breakpoints for ciprofloxacin**

| **Micro-organisms** | **Susceptible (S)** | **Resistant (R)** |
|---|---|---|
| *Staphylococcus* species | S ≤ 1 mg/L | R >1 mg/L |
| *Streptococcus pneumoniae* | S ≤ 0.12 mg/L | R > 2 mg/L |
| *Haemophilus influenzae* | S ≤ 0.5 mg/L | R > 0.5 mg/L |
| *Moraxella catarrhalis* | S ≤ 0.5 mg/L | R > 0.5 mg/L |
| *Pseudomonas aeruginosa* | S ≤ 0.5 mg/L | R > 1 mg/L |

**Pharmacokinetics (PK)**

Following topical administration in the ear, the systemic absorption can be considered as negligible. The plasma levels were not measurable 1 hour after administration of the drops in the ear, even if the eardrum was perforated.

**Absorption**

Ciloxan Eye drops is rapidly absorbed into the eye following topical ocular administration. The systemic levels in humans were low following topical ocular administration. Plasma levels of ciprofloxacin in human subjects following 2 drops of 0.3% ciprofloxacin solution every 2 hours for two days and then every four hours for 5 days ranged from non-quantifiable (<1 ng/mL) to 4.7 ng/mL. The mean peak ciprofloxacin plasma level obtained in this study is approximately 450-fold less than that seen following a single oral dose of 250 mg ciprofloxacin.

**Distribution**

The systemic pharmacokinetic properties of ciprofloxacin have been well studied. Ciprofloxacin widely distributes to tissues of the body. The apparent volume of distribution at steady state is 1.7 to 5.0 L/kg. Serum protein binding is 20-40%.

**Biotransformation/Metabolism**

Both ciprofloxacin and its four primary metabolites are excreted in urine and feces. Renal clearance accounts for approximately two-thirds of the total serum clearance with biliary and fecal routes accounting for the remaining percentages.

**Elimination**

The half-life of ciprofloxacin in serum is 3-5 hours.

**Renal impairment**

In patients with impaired renal function, the elimination half-life of ciprofloxacin is only moderately increased due to extrarenal routes of elimination.

**Hepatic impairment**

In patients with severely reduced liver function, the elimination half-life is only slightly longer.

## 12 Non-clinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

### 13 Pharmaceutical information

**Incompatibilities**
Alkaline solutions (bases).

**Special precautions for storage**
Store at or below 30° C. Protect from light. Keep out of reach of children.
Do not refrigerate or freeze.
Ciloxan Eye / Ear drops must be kept out of the reach and sight of children
Information might differ in some countries

**Instructions for use and handling**

No special requirements.

**Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

**Nature and contents of container**
5 ml plastic bottle dispenser

**Novartis Pharma AG, Basel, Switzerland**