CILOXAN®

3 mg/g eye ointment (Ciprofloxacin)

1 Tradename(s)

CILOXAN® (ciprofloxacin) 3 mg/g Eye ointment

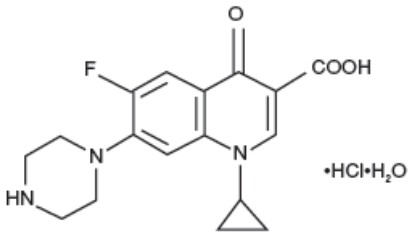
2 Description and Composition

Pharmaceutical form(s)
Sterile eye ointment
White to off-white, homogeneous ointment

Active substances(s)

1 g of ointment contains 3.5 mg ciprofloxacin hydrochloride monohydrate equivalent to 3 mg ciprofloxacin base.

Ciprofloxacin is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 385.8.
Its empirical formula is $C_{17}H_{18}FN_3O_3$•HCl•H_2O 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.

Excipients

Excipients: Mineral oil (alternative name: liquid paraffin), white petrolatum (alternative name: vaselinum album / white soft paraffin).

3 Indications

Ocular Use:

- Ciloxan Eye Ointment is a synthetic, sterile, multiple dose, antimicrobial for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial.
  Ciloxan Eye Ointment is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of microorganisms listed below:

  Gram-Positive:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus Viridans Group

Gram-Negative:
Haemophilus influenza

4 Dosage regimen and administration

Dosage Regimen
Apply a 1/2" ointment ribbon into the conjunctival sac 3 times a day on the first 2 days, then apply a 1/2" ointment ribbon 2 times a day for the next 5 days.

Special populations

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

Pediatric patients
Safety and effectiveness of CILOXAN Eye Ointment in pediatric patients below the age of two years have not been established.

Geriatric patients (65 years of age or above)
No dosage regimen adjustments is required in patients 65 years of age or above.

Method of administration

Ciloxan Eye ointment

- 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 tube should not touch any surface and should also not come into contact with the eye as this may cause injury to the eye. Keep the tube tightly closed when not in use.
- 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 ointment. Patients should remove contact lenses prior to application and wait at least 15 minutes before reinsertion.
- If more than one topical ophthalmic product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

5 Contraindications

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

6 Warnings and precautions

Ocular use

- For ocular 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. 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 other 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 ointment should be discontinued at the first sign of tendon inflammation.
- In patients with corneal ulcer and frequent administration of Ciloxan eye ointment, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of Ciloxan eye ointment. The precipitate does not preclude the continued application of Ciloxan Eye ointment, 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.
- Ciloxan eye ointment has no or negligible influence on the ability to drive or use machines. However, 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.

7 Adverse drug reactions

Ocular use
Summary of the safety profile

In clinical trials, the most frequently reported adverse drug reactions were ocular discomfort, dysgeusia and corneal deposits occurring approximately in 6%, 3% and 3% of patients, respectively.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug 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 *Rare:* dizziness
Eye disorders	*Common:* corneal deposits, ocular hyperaemia, ocular discomfort *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 *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 *Uncommon:* nausea *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 ointment 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

8 Interactions

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

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk Summary
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.

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.

As a precautionary measure, it is preferable to avoid the use of CILOXAN eye ointment during pregnancy.

9.2 Lactation

Risk Summary
It is not known if ciprofloxacin is transferred into human milk following topical ocular 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 administration of Ciloxan on human fertility. Oral administration in animals does not indicate direct harmful effects with respect to fertility. Although ciprofloxacin and other quinolones may 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.

10 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 tube.

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 been shown to be active against most strains of the following organisms both in vitro and in clinical infections (see section 3).

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:

Bacillus species
Corynobacterium species
Enterococcus faecalis (Many strains are only moderately susceptible)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Streptococcus pyogenes

Gram-Negative:

Acinetobacter caloacetius subsp anitratus
Aeromonas caviae
Aeromonas hydrophilia
Brucella melitensis
Campylobacter coli
Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilius ducreyl
Haemophilius parainfluenza
Klebsiella pneumoniae
Klebsiella oxytoca
Legionella pneumophilia
Moraxella (Branhamella) catarrhalis

Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Pasteurella multocida
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella enteritidis
Salmonella typhi
Shigella sonneli
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 Burkholderia cepacia and some strains of Pseudomonas maltophilia and Stenotrophomonas 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. Organisms resistant to ciprofloxacin may be susceptible to beta-lactams or aminoglycosides.

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

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.

Resistant strains, particularly of MRSA (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Campylobacter jejuni, Neisseria gonorrhoeae, Streptococcus pneumoniae)* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance geographically.

Pharmacokinetics (PK)

Absorption
Ciloxan Eye drops is rapidly absorbed into the eye following topical ocular administration. The systemic levels 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 Clinical studies

In multicenter clinical trials, approximately 75% of the patients with signs and symptoms of bacterial conjunctivitis and positive conjunctival cultures were clinically cured and approximately 80% had presumed pathogens eradicated by the end of treatment (day 7).

13 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.

14 Pharmaceutical Information

Incompatibilities
Not applicable

Special precautions for storage
Store at 2° C to 25° C.
Ciloxan Eye ointment must be kept out of the reach and sight and reach of children.

Instructions for use and handling
No special instructions

Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements

Manufacturer
See folding box

Nature and contents of container
Tube containing 3.5 of ointment.

(Information Issued: Mar 2022.SIN)

Novartis Pharma AG, Basel, Switzerland