1. NAME OF THE MEDICINAL PRODUCT

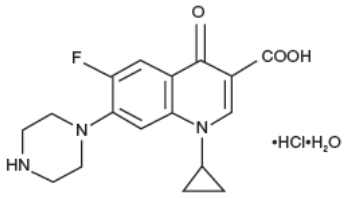
CILOXAN® 0.3% sterile ophthalmic solution
(ciprofloxacin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 3 mg ciprofloxacin base (equivalent to 3.5 mg ciprofloxacin hydrochloride).
Preservative: 1 ml of solution contains 0.06 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

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. It is a faint to light yellow crystalline powder with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$ 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.

3. PHARMACEUTICAL FORM

Sterile ophthalmic solution.
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CILOXAN ophthalmic solution contains ciprofloxacin, a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens.

CILOXAN ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms listed in section 5.1 and in the conditions listed below:

- corneal ulcers
- conjunctivitis.

4.2 Posology and method of administration

Posology

- **Corneal ulcers:** The recommended dosage is 2 drops into the affected eye(s) every 15 minutes for the first 6 hours and then 2 drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill 2 drops in the affected eye(s) hourly. On the third through the fourteenth day, place 2 drops in the affected eye(s) every 4 hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.
- **Bacterial conjunctivitis:** The recommended dosage is 1 or 2 drops instilled into the conjunctival sac of the affected eye(s) every 2 hours while awake for 2 days and 1 or 2 drops every 4 hours while awake for the next 5 days.

Use in children
Safety and effectiveness of CILOXAN ophthalmic solution were determined in 230 children between the ages of 0 and 12 years of age. No serious adverse event was reported in these patients.

Use in patients with hepatic or renal impairment
No studies have been performed using CILOXAN ophthalmic solution in patients with kidney or liver problems.

Method of administration
For ocular use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

Nasolacrimal occlusion or gently closing the eyelid 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.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to other quinolones.

4.4 Special warnings and precautions for use

- For topical ophthalmic 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, dyspnoea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.
- Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines 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. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- 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 ophthalmic solution should be discontinued at the first sign of tendon inflammation.
- In patients with corneal ulcer and frequent administration of CILOXAN ophthalmic solution, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of CILOXAN ophthalmic solution. The precipitate does not preclude the continued application of CILOXAN ophthalmic solution, nor does it adversely affect the clinical course of the recovery process.
- 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 ophthalmic solution. CILOXAN 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 CILOXAN ophthalmic solution and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of CILOXAN ophthalmic solution in pregnant women. Animal studies with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity.

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

Breast-feeding
Ciprofloxacin is excreted in human milk after its oral administration. It is also known that orally administered ciprofloxacin is excreted in the milk of lactating rats. It is unknown whether ciprofloxacin is excreted to human milk following topical ocular administration. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from CILOXAN ophthalmic solution therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
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.

4.7 Effects on ability to drive and use machines

CILOXAN ophthalmic solution 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.

4.8 Undesirable effects

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 reactions
The following adverse reactions have been identified during clinical trials or post-marketing surveillance. These 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) or not known (cannot be estimated from the available data; data from post-marketing surveillance). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Adverse reactions
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
Musculoskeletal and connective tissue disorders	*Not known:* tendon disorder

4.9 Overdose

An ocular overdose of CILOXAN ophthalmic solution may be flushed from the eye(s) with lukewarm tap water.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinfectives, fluoroquinolones. ATC code: S01AE03.

Mechanism of Action
CILOXAN ophthalmic solution 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 is active against a variety of aerobic Gram-positive and Gram-negative bacteria while anaerobic bacteria are less susceptible.

Clinical studies:
Following therapy with CILOXAN ophthalmic solution, more than 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.

Mechanism of Resistance
Fluoroquinolone resistance, particularly ciprofloxacin, requires significant genetic changes in one or more of five major bacterial mechanisms: a) enzymes for DNA synthesis, b) protecting proteins, c) cell permeability, d) drug efflux, or e) plasmid-mediated responses.
Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim and

chloramphenicol. 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.

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. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma mediated resistance has recently been noted. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

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, with topical ciprofloxacin administration as in the case of CILOXAN ophthalmic solution, higher concentrations could be achieved and the drug activity influenced by the physiochemical characteristics at this site of administration. EUCAST breakpoints are not adequate for a topical antibiotic but these recommendations that follow are consistent for general use for commonly recovered ophthalmic pathogens:

Staphylococcus species	S ≤ 1mg/l, R ≥ 1mg/l
Streptococcus pneumonia	S ≤ 0.125mg/l, R ≥ 2mg/l
Haemophilus influenza	S ≤ 0.5mg/l, R ≥ 0.5mg/l
Moraxella catarrhalis	S ≤ 0.5mg/l, R ≥ 0.5mg/l
Pseudomonas aeruginosa	S ≤ 0.5mg/l, R ≥ 1mg/l

Susceptibility to Ciprofloxacin
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. The presentation below lists bacterial species recovered from external ocular infections of the eye.

Commonly susceptible species
Aerobic Gram-positive microorganisms
Corynebacterium accolens
Corynebacterium auris
Corynebacterium propinquum
Corynebacterium psudodiphtheriticum
Corynebacterium striatum
Staphylococcus aureus (methicillin susceptible – MSSA)
Staphylococcus capitis
Staphylococcus epidermidis (methicillin susceptible - MSSE)
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus warneri
Streptococcus pneumoniae
Streptococcus viridans Group
Aerobic Gram-negative microorganisms
Acinetobacter species
Haemophilus influenzae
Moraxella catarrhalis
Pseudomonas aeruginosa
Serratia marcescens

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms:
Staphylococcus aureus (methicillin resistant – MRSA)

Staphylococcus epidermidis (methicillin resistant - MRSE)
Staphylococcus *lugdunensis*

Aerobic Gram-negative micro-organisms*:*
None

Other micro-organisms:
None

Inherently resistant organisms

Aerobic Gram-positive micro-organisms:
Corynebacterium jeikium

Aerobic Gram-negative micro-organisms*:*
Pseudomonas cepacia
Stenotrophomonas maltophilia

Other micro-organisms:
Anaerobes

5.2 Pharmacokinetic properties

Ciprofloxacin ophthalmic solution 0.3% is rapidly absorbed into the eye following topical ocular administration. In rabbits, maximal concentrations in most tissues were attained within 0.5 to 2 hours. Systemic levels are low following topical administration.

Plasma levels of ciprofloxacin in human subjects (N=12) following 2 drops of 0.3% ciprofloxacin solution in each eye every 2 hours while awake for two days and then every four hours while awake for an additional 5 days ranged from non-quantifiable (<1.0 ng/ml) to 4.7 ng/ml. The mean peak ciprofloxacin plasma level obtained in this study (2.6 ± 0.8 ng/ml) is approximately 450-fold less than that seen following a single oral dose of 250 mg ciprofloxacin.

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%. The half-life of ciprofloxacin in serum is 3-5 hours. Both ciprofloxacin and its four primary metabolites are excreted in urine and faeces. Renal clearance accounts for approximately two-thirds of the total serum clearance with biliary and faecal routes accounting for the remaining percentages. In patients with impaired renal function, the elimination half-life of ciprofloxacin is only moderately increased due to extrarenal routes of elimination. Similarly, in patients with severely reduced liver function the elimination half-life is only slightly longer. It has been shown that following co-administration of ciprofloxacin eye drops (0.3%) with diclofenac sodium eye drops (0.1%), there is a minimal effect on the pharmacokinetic profile of ciprofloxacin resulting in a decrease in T_{max} and $AUC_{0\text{-}8h}$.

5.3 Preclinical safety data

Non-clinical data reveal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, sodium acetate trihydrate, acetic acid, mannitol, disodium edetate, hydrochloric acid and/or sodium hydrochloride (to adjust pH), purified water.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze. Protect from light.
Do not use this medicine after the expiry date which is stated on the packaging.
Discard one month after opening.
Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container

Plastic DROP-TAINER® dispenser containing 5 ml.

6.5 Special precautions for disposal

No special requirements.

Manufactured by:

ALCON-COUVREUR
B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland