NOVARTIS

CILOXAN™
(CIPROFLOXACIN)

0.3% Eye drops, solution

Summary of Product Characteristics

Ciloxan™

Antiinfectives; Other antiinfectives

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Eye drops, solution

Active substance

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.

INDICATIONS

Ciloxan Eye drops are indicated for the treatment of corneal ulcers and superficial infections of the eye and adnexa caused by ciprofloxacin susceptible strains of bacteria.

Ciloxan Eye drops is indicated in adults and pediatric patients including neonates, infants, children and adolescents aged 0 to 18 years.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Corneal ulcers

Ciloxan Eye drops must be administered in the following intervals, even during nighttime:

- 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 in the affected eye(s) hourly.
- On the third through the fourteenth day, place two drops in 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.
- A maximum duration of therapy of 21 days is recommended.

Superficial infections of the eye and adnexa

- The usual dose is one or two drops in the affected eye(s) four times a day. In severe infections, the dosage for the first two days may be one or two drops every two hours during waking hours.
- A maximum duration of therapy of 21 days is recommended.

Special populations

Renal and hepatic impairment

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

Pediatric patients (below 18 years)

Ciloxan may be used in pediatric patients at the same dose as in adults.

Geriatric patients (65 years or above)

No dosage regimen adjustment is required in patients 65 years of age or above.

Method of administration

- 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 remove contact lenses prior to application 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.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- For ocular use only.
- 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 preparation, 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 drops should be discontinued at the first sign of tendon inflammation.

- In patients with corneal ulcer and frequent administration of Ciloxan Eye drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of Ciloxan Eye drops. The precipitate does not preclude the continued application 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. Contact lenses must be removed before administration of eye drops and reinserted at least 15 minutes later.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 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 1 Frequency of adverse drug reactions in clinical trials

System organ class	Adverse reactions	Frequency category
Immune system disorders	Hypersensitivity	Rare
Nervous system disorders	Headache	Uncommon
	Dizziness	Rare
Eye disorders	Corneal deposits, ocular hyperaemia, ocular discomfort	Common
	Keratopathy, punctuate 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	Uncommon

	Ocular toxicity, keratitis, corneal epithelium defect, hypoaesthesia eye, diplopia, conjunctivitis, hordeolum, asthenopia, eye irritation, eye inflammation	Rare
Ear and labyrinth disorders	Ear pain	Rare
Respiratory, thoracic and mediastinal disorders	Paranasal sinus hypersecretion, rhinitis	Rare
Gastrointestinal disorders	Dysgeusia	Common
	Nausea	Uncommon
	Diarrhea, abdominal pain	Rare
Skin and subcutaneous tissue disorders	Dermatitis	Rare

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

System organ class	Adverse drug reactions
Musculoskeletal and connective tissue disorders	Tendon disorder

INTERACTIONS

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

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.

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.

It is not likely that the amount of ciprofloxacin would be detectable in human milk or be capable of producing clinical effects in the infant following topical ocular or otic use of the product.

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.

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.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

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 is active against a variety of aerobic Gram-positive and Gram-negative bacteria while anaerobic bacteria are 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 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 ≤ 1mg/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
Non-species related	S ≤ 0.5 mg/L	R > 1 mg/L

Clinical efficacy against specific pathogens

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 micro-organisms:

- *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 micro-organisms:

- *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*

Inherently resistant organisms

Aerobic Gram-positive micro-organisms:

- *Corynebacterium jeikium*

Aerobic Gram-negative micro-organisms:

- *Pseudomonas cepacia*
- *Stenotrophomonas maltophilia*

Other micro-organisms:

- *Anaerobes*

Pharmacokinetics (PK)

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

Biotransformation of ciprofloxacin leads to four metabolites: desethylene ciprofloxacin, sulfonyl ciprofloxacin, oxociprofloxacin and N-acetylciprofloxacin, however the serum concentrations of these metabolites are less than 10% of unchanged ciprofloxacin. 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

Ciprofloxacin is eliminated by the kidneys by an active tubular secretion (60% after an intravenous administration), by metabolism and by the transintestinal route. Following a 100-mg dose of ciprofloxacin given as an intravenous bolus injection, levels of ciprofloxacin were measured in serum, blister fluid, and urine. The mean terminal serum half-life was 4 hours. The 48-hour urinary recovery of ciprofloxacin was about 80%.

Linearity/non-linearity

The rise in peak serum concentrations and the values of the total area under the serum concentration curve were proportional to the increase in oral doses from 100 mg through 1000 mg.

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.

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.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Ciloxan should not be used after the date marked “EXP” on the pack.

Ciloxan must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Manufacturer:

See folding box.

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland