Summary of Product Characteristics
CILOXAN
(Ciprofloxacin 3 mg/mL eye drops, solution)

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1. Name of the medicinal product

CILOXAN (Ciprofloxacin) 3 mg/mL eye drops, solution.

2. Qualitative and quantitative composition

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

Excipient with known effect:

1 mL of solution contains 0.06 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Eye drops, solution.

4. Clinical particulars

4.1 Therapeutic 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 are indicated in adults and paediatric patients, including neonates, infants, children and adolescents aged 0 to 18 years.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology – corneal ulcers

Ciloxan eye drops must be administered at the following intervals, even during the night. Day 1: instil 2 drops into the affected eye(s) every 15 minutes for the first 6 hours, then 2 drops every 30 minutes for the remainder of the day. Day 2: instil 2 drops into the affected eye(s) hourly. Days 3 to 14: instil 2 drops into the affected eye(s) every 4 hours. If treatment is required beyond 14 days, the dosing regimen is at the discretion of the attending physician. A maximum duration of therapy of 21 days is recommended.

Posology – superficial infections of the eye and adnexa

The usual dose is one or two drops into the affected eye(s) four times a day. In severe infections, the dose 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.

Renal and hepatic impairment

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

Paediatric population

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

Elderly

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

Method of administration

For ocular use only. After the cap is removed, if the tamper-evident snap collar is loose it should be removed before using the product. To avoid contamination, the tip of the dropper should not touch any surface or the eye. Nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended, as this may reduce systemic absorption and systemic adverse reactions. Contact lenses should be removed before application and reinserted at least 15 minutes later. If more than one topical ophthalmic product is used, the medicines must be administered at least 5 minutes apart, and eye ointment should be administered last.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Ciloxan should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity; serious acute reactions may require immediate emergency treatment.

As with all antibacterial preparations, prolonged use may lead to overgrowth of non-susceptible bacteria 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. Treatment with Ciloxan should be discontinued at the first sign of tendon inflammation.

In patients with corneal ulcer and frequent administration, white topical ocular precipitates (medication residue) have been observed, which resolved with continued application; the precipitate does not preclude continued use nor interfere with therapeutic response but may delay epithelial healing. Contact-lens wear is not recommended during treatment of an ocular infection.

Benzalkonium chloride

Ciloxan contains benzalkonium chloride, which may cause eye irritation and may discolour soft contact lenses. Contact lenses must be removed before administration and reinserted at least 15 minutes later.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies with Ciloxan in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity, and 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 foetus.

Breast-feeding

It is not known whether ciprofloxacin is transferred into human milk following topical ocular administration; systemically administered ciprofloxacin has been found in human milk. 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.

Fertility

There are no data on 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.

4.7 Effects on ability to drive and use machines

As with other eye drops, transient blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs on instillation, the patient should wait until vision clears before driving or using machines.

4.8 Undesirable effects

The adverse reactions are listed by System Organ Class and frequency, defined as: 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) and not known (cannot be estimated from the available data). Reactions with frequency 'not known' are derived from post-marketing spontaneous reports and literature cases.

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Rare	Hypersensitivity
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, eye hypoaesthesia, 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
Musculoskeletal and connective tissue disorders	Not known	Tendon disorder

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Owing to the characteristics of this preparation, no toxic effects are expected with an ocular overdose, nor in the event of accidental ingestion of the contents of one bottle. A topical overdose may be flushed from the eye(s) with lukewarm water.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, anti-infectives, fluoroquinolones. ATC code: S01AX13.

Mechanism of action

Ciloxan contains the fluoroquinolone ciprofloxacin. Its bactericidal activity results from inhibition of the bacterial enzymes DNA gyrase (topoisomerase II) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination, ultimately resulting in cell death. The bactericidal activity of ciprofloxacin is concentration-dependent, with higher kill rates 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 ciprofloxacin can be acquired through a stepwise process by target-site mutation in both DNA gyrase and topoisomerase IV. Impermeability and/or active efflux-pump mechanisms may also affect susceptibility, and plasmid-mediated resistance encoded by qnr genes has been reported. Because fluoroquinolones differ in structure and mode of action from aminoglycosides, beta-lactams, macrolides, tetracyclines, sulfonamides, trimethoprim and chloramphenicol, organisms resistant to those agents may remain susceptible to ciprofloxacin.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time, and local information on resistance is desirable. Commonly susceptible species recovered from external ocular infections include methicillin-susceptible Staphylococcus aureus and coagulase-negative staphylococci, Streptococcus pneumoniae, viridans-group streptococci, Corynebacterium species, Haemophilus influenzae, Moraxella catarrhalis, Acinetobacter species, Pseudomonas aeruginosa and Serratia marcescens. Species for which acquired resistance may be a problem include methicillin-resistant staphylococci. Inherently resistant organisms include Stenotrophomonas maltophilia, Burkholderia cepacia and anaerobes.

5.2 Pharmacokinetic properties

Absorption

Ciloxan is rapidly absorbed into the eye following topical ocular administration, while systemic levels are low. Following 2 drops of 0.3% ciprofloxacin every 2 hours for two days and then every four hours for 5 days, plasma levels ranged from non-quantifiable (< 1 ng/mL) to 4.7 ng/mL — approximately 450-fold lower than after a single oral dose of 250 mg ciprofloxacin.

Distribution

Ciprofloxacin is widely distributed to body tissues; the apparent volume of distribution at steady state is 1.7 to 5.0 L/kg and serum protein binding is 20–40%.

Biotransformation

Biotransformation yields four metabolites (desethylene-, sulfonyl-, oxo- and N-acetyl-ciprofloxacin), whose serum concentrations are less than 10% of unchanged ciprofloxacin.

Elimination

Ciprofloxacin is eliminated by the kidneys through active tubular secretion, by metabolism and by the transintestinal route; the mean terminal serum half-life is about 4 hours. In renal or hepatic impairment, the elimination half-life is only moderately or slightly increased owing to extrarenal routes of elimination.

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 sufficiently in excess of the maximum human exposure to indicate little relevance to clinical use.

6. Pharmaceutical particulars

6.1 List of excipients

- Benzalkonium chloride
- Disodium edetate
- Mannitol
- Acetic acid
- Sodium acetate trihydrate
- Hydrochloric acid and/or sodium hydroxide (for pH adjustment)
- Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months. After first opening, the contents should be used within 28 days.

6.4 Special precautions for storage

Do not refrigerate or freeze. Do not store above 30°C. Keep out of the reach and sight of children.

6.5 Nature and contents of container

Plastic dropper bottle (DROP-TAINER) with a dispensing tip and screw cap, presented in a carton with the package insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland.

Manufacturer

Novartis Manufacturing NV, Rijksweg 14, 2870 Puurs-Sint-Amands, Belgium.

8. Marketing Authorisation Number

H96/647

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text