NOVARTIS

CILOXAN® Eye Drops

Each 1,0 ml solution contains ciprofloxacin hydrochloride equivalent to ciprofloxacin 3,0 mg

CILOXAN® Eye Ointment

Each 1,0 g ointment contains ciprofloxacin hydrochloride equivalent to ciprofloxacin base 3,0 mg

Professional Information

Document status: Final

Release date: 30 November 2021

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CILOXAN® Eye Drops (3 mg/ml ciprofloxacin, solution)

CILOXAN® Eye Ointment (3 mg/g ciprofloxacin)

2 QUALITIVE AND QUANTITIVE COMPOSITION

CILOXAN® Eye Drops contains ciprofloxacin hydrochloride equivalent to 3 mg/ml ciprofloxacin

Preservative: Benzalkonium chloride 0,006 % (*m/v*).

CILOXAN® Eye Ointment contains ciprofloxacin hydrochloride equivalent to 3 mg/g ciprofloxacin in an anhydrous ophthalmic ointment base.

It does not contain a preservative.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

CILOXAN® Eye Drops: Colourless, clear solution.

CILOXAN® Eye Ointment: Homogenous, white to off-white ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- CILOXAN® Eye Drops and Eye Ointment are indicated for the treatment of corneal ulceration and conjunctivitis caused by susceptible strains of bacteria.
- Appropriate monitoring of bacterial response to topical antibacterial therapy should accompany the use of CILOXAN® Eye Drops and Eye Ointment.

4.2 Posology and method of administration

Posology

The recommended dosage regimens for adults and children over the age of two years are as follows:

- **Corneal ulcers or abscesses**:

CILOXAN® Eye Drops: On the first day, instil two drops into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the day. On the second day, instil two drops in the affected eye hourly. On the third through the fourteenth day, instil two drops into the affected eye every four hours. If the patient needs to be treated longer than 14 days, the dosing regimen is at the discretion of the physician.

CILOXAN® Eye Ointment: Apply 1,25 cm into the conjunctival sac every 1-2 hours around the clock for two days, then every four hours for a further 12 days. The dosing may be extended at the discretion of the physician.

- **Bacterial conjunctivitis:**

CILOXAN® Eye Drops: Instil one or two drops into the conjunctival sac(s) every two hours while awake for two days, then one or two drops every four hours while awake until the bacterial infection is resolved.

CILOXAN® Eye Ointment: Apply 1,25 cm into the conjunctival sac (or on the lid margin, respectively) three times daily for two days, then twice daily for a further five days. The dosing may be extended at the discretion of the physician.

Method of administration

For ocular use.

4.3 Contraindications

- Hypersensitivity to ciprofloxacin or any component of this medication.
- Hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

4.4 Special warnings and precautions for use

- CILOXAN® Eye Drops and Eye Ointment should be discontinued at the first appearance of a skin rash or any other sign of a hypersensitivity reaction. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving systemic quinolone therapy. 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. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

- Prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate measures should be initiated. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy and where appropriate, fluorescein staining.
- As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.
- Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and those treated concurrently with corticosteroids. Therefore, treatment with CILOXAN should be discontinued at the first sign of tendon inflammation (*see section 4.8*).
- In patients with corneal ulcer and frequent administration of CILOXAN, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of CILOXAN. The precipitate does not preclude the continued application of CILOXAN nor does it adversely affect the clinical course of the recovery process. The onset of the precipitate was within 24 hours to 7 days after starting therapy. Resolution of the precipitate varied from immediately to 13 days after therapy commencing.

- 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.
- CILOXAN® Eye Drops contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. In case patients are allowed to wear contact lenses they should be instructed to remove them prior to application of CILOXAN® Eye Drops and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicines and other forms of interaction

The systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effect of warfarin and its derivatives and transient increases in serum creatinine have been observed in patients receiving cyclosporin concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Safety in pregnant women has not been established.

Breastfeeding

Safety in pregnant women and breastfeeding mothers has not been established.

Fertility

Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin on fertility.

4.7 Effects on ability to drive and use machines

CILOXAN® Eye Drops and Eye Ointment can cause blurred vison or other visual disturbances (*see section 4.8 Undesirable effects*) and may have no or negligible influence or effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

In clinical trials with CILOXAN® Eye Drops and Eye Ointment, the following treatment-related signs and symptoms have been reported:

a. Summary of the safety profile

The following adverse reactions have been reported during clinical trials with CILOXAN® Eye drops / CILOXAN® Eye ointment, and 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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Common	Uncommon	Rare
Immune system disorders:			hypersensitivity
Nervous system disorders:		headache	dizziness
Eye disorders:	white precipitate and ocular discomfort (stinging and burning	keratopathy/punctuate keratitis, corneal infiltrates, photophobia,	ocular toxicity, keratitis, conjunctivitis, corneal epithelium defect,

	may occur upon application), ocular hyperaemia	reduced visual acuity, lid oedema, blurred vision, eye pain, decreased tearing, eye swelling, pruritis, (itching), increased tearing, eye discharge, lid margin crusting, crystals/scales, conjunctival oedema, erythema of eyelid	diplopia, hypoaesthesia eye, asthenopia, hordeolum, eye irritation, eye inflammation
Ear and labyrinth disorders:			ear pain
Respiratory, thoracic and mediastinal disorders:			paranasal sinus hypersecretion,rhinitis
Gastrointestinal disorders:	taste perversion (metallic taste)	nausea	diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders:			dermatitis

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Body System	**Undesirable effect**
Musculoskeletal, connective tissue and bone disorders:	tendon disorder

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are

asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8*).

A topical ocular overdose may be flushed from the eye(s) with lukewarm tap water.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic Group – Ophthalmologicals, Other Anti-infective, ATC Code: S01A X13.

Mechanism of action

Ciprofloxacin is a broad-spectrum water-soluble fluoroquinolone antibacterial. It has cidal and inhibitory activities against bacteria, which result from an interference with the DNA gyrase, an enzyme required by the bacterium for the synthesis of DNA. Thus, the vital information from the bacterial chromosomes cannot be transcribed any longer, which causes a breakdown in the bacterial metabolism. Ciprofloxacin has an *in vitro* activity against a wide range of Gram-negative microorganisms.

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 aminoglycoside 6'-N-acetyltransferase, AAC (6')-Ib.

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:

There are no official topical ocular breakpoints for ciprofloxacin and although systemic breakpoints have been used, their relevance to topical therapy is doubtful. The EUCAST clinical MIC breakpoints used for this antibiotic are the following:

Staphylococcus species	S ≤ 1mg/l, R ≥ 1mg/l
Streptococcus pneumoniae	S ≤ 0.125mg/l, R ≥ 2mg/l
Haemophilus influenzae	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

Inherently resistant organisms
Aerobic Gram-positive micro-organisms: *Corynebacterium jeikium* **Aerobic Gram-negative micro-organisms:** None **Other micro-organisms:**

None

5.2 Pharmacokinetic properties

Ciprofloxacin is absorbed systemically after topical ocular administration. The maximum reported plasma concentration of ciprofloxacin was less than 5 ng/ml (some 450-fold less than levels observed following simple 250 mg oral administration) and the mean plasma concentration was less than 2,5 ng/ml.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CILOXAN Eye drops:

Benzalkonium chloride; disodium edetate; mannitol; acetic acid; sodium acetate trihydrate; hydrochloric acid; sodium hydroxide; purified water.

CILOXAN Eye ointment:

Liquid paraffin; white soft paraffin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened 24 months.

CILOXAN Eye drops:

Do not use more than 30 days after opening.

6.4 Special precautions for storage

CILOXAN® Eye Drops:

Store at or below 25 °C.

Do not refrigerate or freeze.

CILOXAN® Eye Ointment:

Do not refrigerate.

Store at or below 25 °C.

Store in the original package/container.

6.5 Nature and contents of container

CILOXAN® Eye Drops: Low-density polyethylene bottle containing 5 ml sterile eye drops.

CILOXAN® Eye Ointment: Epoxy-phenolic lined aluminium tube containing 3,5 g sterile eye ointment, with white high-density and/or low-density polyethylene nozzle (dispensing tip) and white high-density polyethylene tube closure. The text is preprinted on the tube.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

8 REGISTRATION NUMBER(S)

CILOXAN® Eye Drops: Z/15.1/202

CILOXAN® Eye Ointment: 35/15.1/0410

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CILOXAN® Eye Drops: 30 September 2011

CILOXAN® Eye Ointment: 22 November 2013

10 DATE OF REVISION OF TEXT

CILOXAN® Eye Drops: 30 November 2021

CILOXAN® Eye Ointment: 30 November 2021

Ciloxan® Eye Drops

Botswana: S2

Reg. No.: BOT0701051

Namibia: NS2

Reg. No.: 06/15.1/0181

Zimbabwe: PP

Reg. No.: 99/19.1.1/3585

Ciloxan® Eye Ointment

Botswana: S2

Reg. No.: BOT0701052

Namibia: NS2

Reg. No.: 06/15.1/0180