1. NAME OF THE MEDICINAL PRODUCT

CILOXAN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 3 mg of ciprofloxacin (as hydrochloride).
Excipient with known effect: this medicine contains 0.06 mg of benzalkonium chloride in each ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye and ear drops, solution.
A clear and colorless to pale yellow solution provided in a plastic bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Corneal ulcers and conjunctivitis caused by susceptible gram positive and gram negative microorganisms for adults and pediatric patients above the age of 1 year.
For localized or diffuse otitis externa accompanied by a strong inflammatory reaction and of which the strains are susceptible to ciprofloxacin, and for the acute flare-up of a chronic otitis media.
In this case, a mucopurulent secretion comes through the perforated eardrum. Pseudomonas aeruginosa is one of the organisms most likely to be found in this case .
Also in other infections of the ear in which Pseudomonas aeruginosa and/or other susceptible strains may be demonstrated or suspected (for example with suppurating tympanic tubes), Ciloxan can be used under the strict supervision of an ear specialist. It must be understood that this is not a routine treatment and that improper use must be avoided.

4.2 Posology and method of administration

Ocular use:
Adults and children 1 year and above.

Posology

Corneal ulcers
CILOXAN should be administered at the following intervals, even at night:

- Day 1: instil 2 drops into the affected eye every 15 minutes for the first 6 hours and then 2 drops every 30 minutes for the remainder of the day.
- Day 2: instil 2 drops into the affected eye every hour.
- Days 3 to 14: instil 2 drops into the affected eye every 4 hours.
- If the treatment lasts longer than 14 days, the amounts can be adjusted at the discretion of the treating physician.

Superficial bacterial infections of the eye and adnexa
For the first 2 days instil 1 or 2 drops into the conjunctival sac of the infected eye(s) every 2 hours during the day. Then 1 or 2 drops every 4 hours during the day until the bacterial infection has resolved.

Method of administration

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 of the bottle. Keep the bottle tightly closed when not in use.

When using multiple ophthalmic preparations, an interval of at least 5 minutes should be left between successive administrations. Eye ointments should be administered last, see section 4.5.

Otic use:
Posology

Adults and children over 1 year old:
First thoroughly clean the external auditory duct. lt is more agreeable to administer the solution at room temperature and better still at body temperature to prevent vestibular stimulation. Instil the product into the external ear duct as follows: 3 to 4 drops, two to four times per day, or more frequently, if required. The patient should first lie on the opposite side in relation to the affection and should preferably remain lying in this position for five to ten minutes. After local cleaning, an impregnated tent of gauze or a hydrophylic tent of cotton can also be inserted in the ear duct, and is generally left in place for one to two days, but should be impregnated to saturation with the product two times per day. In general, the duration of treatment does not exceed five to ten days.
Sometimes, the treatment can be prolonged, but in those cases it is best the
susceptibility of the local flora be established. As with all antibacterial preparations,
prolonged use may lead to overgrowth with non-susceptible micro-organisms or fungi.
For either indication a maximum duration of therapy of 21 days is recommended.

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General:
- For ocular or otic use only. Do not inject or swallow.
- Serious and occasionally fatal (anaphylactic) hypersensitivity reactions, some following the first dose, have been 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.

- Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen administration and airway clearance should be undertaken if clinically required.
- Ciprofloxacin should be discontinued at the first appearance of skin rash or any other sign of a hypersensitivity reaction.
- As with all antibacterial preparations, prolonged use may lead to proliferation of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate treatment should be initiated.
- Tendon inflammation and rupture may occur during systemic treatment with fluoroquinolones, including ciprofloxacin, especially in elderly patients and those treated concurrently with corticosteroids. Therefore, treatment with CILOXAN eye and ear drops should be discontinued at the first sign of tendon inflammation (see section 4.8 Undesirable effects).

Ocular use:
- Clinical experience is very limited in children under 1 year old, particularly neonates.
- The use of CILOXAN eye drops in neonates with ophthalmia neonatorum caused by gonococci or chlamydia is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition.
- When using CILOXAN eye drops, the risk of rhinopharyngeal passage, which may contribute to the development and spread of bacterial resistance, should be taken into account.
- The patient should be examined with a slit lamp whenever this is indicated by the clinical evaluation.
- A white topical ocular precipitate (medication residue) was observed in corneal ulcer patients who frequently used CILOXAN eye drops. This resolved after further administration of CILOXAN eye drops. This precipitate does not preclude continued use of CILOXAN, nor does it adversely effect the further course of the recovery process.
- The wearing of contact lenses is not recommended during treatment of an eye infection. Patients should therefore be advised not to wear contact lenses during treatment with CILOXAN eye drops.
- This medicine contains 0.3 mg of benzalkonium chloride in each 5 ml, equivalent to 0.06 mg/ml. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the lenses. In case patients are allowed to wear contact lenses, they should be instructed to remove them before applying CILOXAN eye drops and to wait at least 15 minutes before reinserting them. Benzalkonium chloride can also cause eye irritation, particularly if the patient has dry eyes or a corneal disorder.
- If CILOXAN is used in the eye, the following measures are useful for reducing systemic absorption after application of the eye drops:
  - Keep the eyelid closed for 2 minutes.
  - Press on the tear duct with a finger for 2 minutes.

Otic use:
- Efficacy and safety in children under 1 year old have not been established. The safety and efficacy of this product in children aged 1 year and above have been established in controlled clinical trials. Although very limited data are available in children under 1 year old treated for acute otitis externa, there are no differences in the disease process in this patient population that would preclude the use of this product in patients under 1 year old. Based on these very limited data, the treating physician should weigh the clinical benefits of use against the known and possibly unknown risks when prescribing the product for children under 1 year old.
- Careful and frequent medical surveillance is required during otic use in order to identify a possible need for other therapeutic measures in timely fashion.
- CILOXAN ear drops contain benzalkonium chloride, which may be irritant and cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Given the low systemic concentration of ciprofloxacin when applied topically to the eye or ear, drug interactions are unlikely to occur.

If multiple ophthalmic preparations are used, the products should be administered at least 5 minutes apart. Eye ointments should be administered last.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or only limited data on the use of CILOXAN in pregnant women. The results of animal studies with orally administered ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity (see section 5.3). Systemic exposure to ciprofloxacin after topical use is expected to be low. As a precaution, it is preferable to avoid the use of CILOXAN during pregnancy unless the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Lactation
Ciprofloxacin is excreted in human milk after oral administration. It is not known whether ciprofloxacin enters human milk after topical ocular or otic administration. A risk to breast-fed infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue or not initiate treatment with CILOXAN, taking into account the benefit of breast-feeding to the child and the benefit of treatment to 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 has no or negligible influence on the ability to drive and use machines.

As with all eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurred vision occurs following application, the patient must wait until the vision clears before driving or operating machinery.

There are no known effects of CILOXAN ear drops on the ability to drive and use machines.

4.8 Undesirable effects

Ocular use

Summary of the safety profile
The most common adverse drug reactions observed in clinical trials were ocular discomfort, dysgeusia and corneal deposits occurring in approximately 6%, 3% and 3% of patients, respectively.

Tabulated summary of adverse reactions

The following adverse reactions are ranked according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be determined from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. The adverse reactions were identified during clinical trials and post-marketing experience.

After ocular use:

System Organ Class	MedDRA Preferred Term (v. 15.1)
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

Paediatric patients
The safety and efficacy of CILOXAN were determined in 230 children aged between 0 and 12 years. No serious adverse reactions have been reported in this patient population.

Otic use
The most common adverse drug reactions observed in clinical trials were ear pruritus and otorrhoea, occurring in approximately 1% of patients.

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. The adverse reactions were identified during clinical trials and post-marketing experience. For a description of the frequency conventions, see above.

After otic use:

System Organ Class	MedDRA Preferred Term (v. 15.1)
Nervous system disorders	Uncommon: headache
Ear and labyrinth disorders	Uncommon: ear pain, ear congestion, otorrhoea, ear pruritus Not known: tinnitus
Skin and subcutaneous tissue disorders	Uncommon: dermatitis
General disorders and administration site conditions	Uncommon: pyrexia

Paediatric patients

The safety and efficacy of CILOXAN were determined in 193 children aged between 0 and 12 years. No serious adverse reactions have been reported in this patient population.

Description of selected adverse reactions

Ocular use
With topically applied fluoroquinolones, (generalised) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely. In isolated cases, blurred vision, decreased visual acuity and medication residue have been observed with ophthalmic ciprofloxacin.

A white topical ocular precipitate (medication residue) was observed in patients with corneal ulcer and frequent administration of CILOXAN eye drops. This resolved after further administration of CILOXAN eye drops. This precipitate does not preclude continued use of this product and does not adversely effect the clinical course of the recovery process.

Otic use
The ingredients rarely cause hypersensitivity with otic use. However, as with any substance applied to the skin, an allergic reaction to one of the components of the medicinal product is always possible.

Ocular and otic use
Serious and occasionally fatal (anaphylactic) hypersensitivity reactions, some following the first dose, have been observed 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.

Ruptures of the Achilles, shoulder, hand or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post-marketing experience with systemic fluoroquinolones indicate that the risk of such tendon ruptures may be increased in patients receiving corticosteroids, especially in geriatric patients and in tendons under high stress, including the Achilles tendon. To date, clinical and post-marketing data have not demonstrated a clear association between topical CILOXAN and musculoskeletal and connective tissue adverse reactions.

Moderate to severe phototoxicity has been observed in patients treated with systemic quinolones. Nevertheless, phototoxic reactions to ciprofloxacin are uncommon.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online formhttps://sideeffects.health.gov.il, and to Novartis using the following email address: safetydesk.israel@novartis.com.

4.9 Overdose

Symptoms:
No cases of overdose have been reported.
Due to the characteristics of this preparation, no toxic effects are expected with an ocular/otic overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

Treatment:
In case of topical overdose, CILOXAN may be rinsed from the eye with lukewarm tap water.
Treatment of any exposure is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-infectives, other anti-infectives, ATC code: S03 AA 07

Mechanism of action
CILOXAN contains the fluoroquinolone ciprofloxacin. The bactericidal and bacteriostatic effect of ciprofloxacin results from interference with DNA gyrase, an enzyme used by the bacterium for the synthesis of DNA. As a result, the vital information of the bacterial chromosomes can no longer be transmitted, causing a breakdown in the metabolism of the bacteria. Ciprofloxacin is active *in vitro* against a broad spectrum of Gram-positive and Gram-negative bacteria.

PK/PD relationship
The efficacy of an antibacterial agent in the cornea depends not only on the MIC90 for the organism, but on the drug content in the stromal cells. Metal ions in eye irrigation solutions can markedly decrease the bioavailability of fluoroquinolones. As a result, the clinical efficacy of ciprofloxacin against deep ocular infections may not be as good as laboratory antimicrobial susceptibility testing would indicate due to the drug's interaction with the metal ions.

Clinical efficacy against specific pathogens
See “Susceptibility to ciprofloxacin” below.

Antibacterial effect against other relevant pathogens
See “Mechanism of resistance” below.

Mechanism of resistance
Resistance to fluoroquinolones, particularly ciprofloxacin, requires significant genetic changes in one or more of five major bacterial mechanisms: a) enzymes for DNA synthesis, b) protective 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 mechanism 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 breakpoints for topical use of ciprofloxacin. Use is made of breakpoints based on systemic administration, but it is doubtful whether they apply to topical use. The EUCAST clinical MIC breakpoints for this antibiotic are the following:

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

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. If 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. Bacterial species recovered from external eye infections are listed below.

Commonly susceptible species
Aerobic Gram-positive microorganisms
Corynebacterium accolens
Corynebacterium auris
Corynebacterium propinquum
Corynebacterium pseudodiphtheriticum
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 microorganisms:
Staphylococcus aureus (methicillin-resistant – MRSA)
Staphylococcus epidermidis (methicillin-resistant – MRSE)
Staphylococcus lugdunensis
Aerobic Gram-negative microorganisms:
None
Other microorganisms
None

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

Paediatric patients

Ocular use
The safety and efficacy of CILOXAN 3 mg/ml eye drops were determined in 230 children aged between 0 and 12 years. No serious adverse reactions have been reported in this patient population.

Otic use
The safety and efficacy of CILOXAN 3 mg/ml ear drops were determined in 193 children aged between 0 and 12 years. No serious adverse reactions have been reported in this patient population.

Data from clinical trials
Clinical trial data are summarised in section 4.8.

5.2 Pharmacokinetic properties

Ocular use:
Ciprofloxacin is rapidly absorbed into the eye after topical ocular administration of CILOXAN 3 mg/ml eye drops, solution. In rabbits, maximum concentrations were reached in most tissues within 0.5 to 2 hours. Systemic concentrations are low after topical administration. Plasma levels of ciprofloxacin in humans after 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 (<1.0 ng/ml) to 4.7 ng/ml. The mean peak ciprofloxacin plasma level obtained in this study is approximately 450 times less than that observed after a single oral administration of 250 mg ciprofloxacin. The systemic pharmacokinetic properties of ciprofloxacin have been well studied. Ciprofloxacin is widely distributed to body tissues. 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 is approximately two-thirds of total serum clearance, with the biliary and faecal routes of excretion accounting for the remaining percentages. In patients with renal impairment, the elimination half-life of ciprofloxacin is only moderately increased due to extrarenal routes of elimination. Similarly, the elimination half-life is only slightly longer in patients with severe hepatic impairment.

Ocular pharmacokinetics and systemic exposure levels of ciprofloxacin after topical ocular administration of CILOXAN 3 mg/g eye ointment have not been studied.

Otic use:
In children with otitis media with tympanostomy tubes treated with ciprofloxacin 3 mg/ml solution (3 drops 3 times daily for 14 days), no plasma concentrations of ciprofloxacin were detected (limit of quantification 5 ng/ml) [Force, RW 1995]. In children with purulent otitis with perforated eardrum treated with ciprofloxacin 2 mg/ml solution (twice daily for 7 to 10 days), no circulating plasma concentration of ciprofloxacin was detected up to the quantification limit of 5 ng/ml. No significant systemic passage of ciprofloxacin is expected under normal use.

No pharmacokinetic data are available with regard to use in children.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only after exposure considered to be significantly higher than maximum human exposure, and are therefore of little clinical relevance.

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested after oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal. A one-month topical ocular study of ciprofloxacin 3 mg/ml eye drops, solution in immature beagles did not reveal any joint lesions. There is also no evidence that the ophthalmic dosage form has any effect on weight-bearing points.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, disodium edetate, acetic acid (6N), sodium acetate trihydrate, benzalkonium chloride, hydrochloric acid, sodium hydroxide, purified water

6.2 Incompatibilities

Incompatible with alkaline solutions (bases).

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening can be used for 28 days.

6.4 Special precautions for storage

Store below 25°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

5 ml dropper container.

6.6 Special precautions for disposal

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

7. REGISTRATION HOLDER AND IMPORTER:

Novartis Israel Ltd., P.O.B 7126, Tel Aviv,Israel.

8. MARKETING AUTHORISATION NUMBER

061-17-27635-00

Revised in March 2025.