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CILOXAN®

3 mg/ml, eye and ear drops, solution

1. NAME OF THE MEDICINAL PRODUCT

CILOXAN®, 3 mg/ml, eye and ear drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciprofloxacin hydrochloride 3.5 mg/ml (equiv. 3 mg/ml base)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Eye and ear drops, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CILOXAN® is indicated in the treatment of corneal ulcers and superficial infections of the eye and its adnexa, caused by strains presumed or reported susceptible to ciprofloxacin, in specific *Pseudomonas aeruginosa* and other gram-negative organisms resistant to common treatments.
CILOXAN® is also indicated for a local or diffuse otitis externa accompanied by a strong inflammatory reaction caused by strains that are susceptible to ciprofloxacin, as for a sudden flare-up of a chronic otitis media. In this case, a mucopurulent secretion passes through the perforated eardrum. *Pseudomonas aeruginosa* is one of the most likely organisms to be found here. Also in case of other ear inflammations in which *Pseudomonas aeruginosa* and/or other susceptible germs (e.g. in the case of suppurating tympanic tubes) may be demonstrated or suspected, CILOXAN® can be used under the strict supervision of an ear specialist. One should realise that it does not involve a routine treatment here, so improper use must be avoided.

4.2 Posology and method of administration

Corneal ulcers:
CILOXAN® must be administered in the following intervals, even during night time:

On the 1st day: instil 2 drops into the affected eye every 15 minutes for the first six hours; and then 2 drops into the affected eye every 30 minutes for the remainder of the day.

On the 2nd day: instil 2 drops into the affected eye hourly.

On the 3rd through the 14th day, put two drops in the affected eye every 4 hours. If treatment is to surpass 14 days, the quantities can be adapted to the wishes of the attending physician.

Superficial bacterial infections of the eye and its adnexa:
For the first 2 days instil 1 or 2 drops into the conjunctival sac of the infected eye(s) every 2 hours while awake. Then 1 or 2 drops every 4 hours while awake until the bacterial infection is resolved.

Otic use:

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First thoroughly clean the external auditory duct. It 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.

4.3 Contraindications

Hypersensitivity to ciprofloxacin hydrochloride or to one of the excipients. The use of CILOXAN® is also contraindicated in patients with hypersensitivity to other medicines of the same chemical group (quinolones).

4.4 Special warnings and precautions for use

As with other antibacterial preparations, prolonged use of ciprofloxacin may lead to the formation of resistant organisms, including fungi. In case of a superinfection an adjusted treatment should be started. Whenever it is required for the clinical evaluation (ophthalmological use), the patient is to be examined with a slit lamp.
Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systemically administered quinolones.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine (adrenaline) and other resuscitation measures, such as the administration of oxygen, intravenous solutions, intravenous antihistaminics, corticoids, vasopressors and artificial respiration, when clinically necessary.

As CILOXAN® contains the preservative benzalkonium chloride, this may cause eye irritation and is known to discolor soft contact lenses. Therefore, patients must remove contact lenses prior to application of CILOXAN® and be instructed to wait 15 minutes after instillation of CILOXAN® before inserting contact lenses. Patients should be advised not to wear contact lenses in the presence of ocular infection.

If CILOXAN® is applied in the eye, following measures are useful to reduce systemic resorption after application of the eye drops:
- Keep the eyelid closed for 2 minutes.
- Close the lachrymal duct with the finger for 2 minutes.

In otic use, meticulous medical monitoring is also required in order to be able to timely determine the possible necessity of other therapeutic measures (systemic antibiotics, surgery, etc.)

4.5 Interaction with other medicinal products and other forms of interaction

Specific studies with regard to the interactions were not conducted for ophtalmologic ciprofloxacin. It was however demonstrated that the systemic administration of certain quinolones increased the plasma concentrations of theophylline, had an influence on the metabolism of caffeine, and intensified the action of the oral anticoagulant warfarin and its derivatives. A temporary increase of creatinine in the serum was reported in patients who concomitantly received cyclosporin and systemic ciprofloxacin.

If supplementary eye preparations are to be used, one should wait about 15 minutes between two applications.

4.6 Pregnancy and lactation

Pregnancy
As there are no controlled studies in pregnant women, CILOXAN® should be used during pregnancy only if the benefit justifies the possible risk for the foetus.

Lactation
The excretion of ciprofloxacin in human milk after topical administration in the eye has not been studied. Therefore caution should be observed when CILOXAN® is used while breast-feeding.

4.7 Effects on ability to drive and use machines

As with any eye drop, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

No effects on the ability to drive or use machines are expected with otic use.

4.8 Undesirable effects

Following use in the eye:

Eye Disorders
Common (≥ 1% < 10%): eye irritation, ocular discomfort, eye pruritus, abnormal sensation in eye, eyelid margin crusting, ocular hyperaemia.
Uncommon (≥ 0.1% < 1%): keratopathy, keratitis, eye allergy, eyelid oedema, lachrymation increased, photophobia, corneal infiltrates, visual acuity reduced.

Gastrointestinal Disorders
Uncommon (≥ 0.1% < 1%): nausea.

Immune System Disorders
Very rare (< 0.01%): hypersensitivity (systemic).

Injury, Poisoning and Procedural Complications
Uncommon (≥ 0.1% < 1%): medication residue*.

Nervous System Disorders
Common (≥ 1% < 10%): dysgeusia.

*In patients with corneal ulcer and frequent administration of CILOXAN®, white precipitates (medication residue) have been observed more commonly (up to 17% of patients) which resolved after continued application of CILOXAN®. The precipitate does not preclude continued use of CILOXAN®, nor does it adversely affect the clinical course of the recovery process.

Following use in the ear:

Immune System Disorders
Rare (≥ 0.01% < 0.1%): hypersensitivity.

4.9 Overdose

In case of topical overdose of CILOXAN®, eliminate the overdose with tepid water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-infectives, other anti-infectives

ATC code: S 03 AA 07

CILOXAN® contains ciprofloxacin hydrochloride and is specifically intended for ophthalmic and otic use. This solution is ideal for the treatment of disorders for which a local, non-general effect is preferable.
Ciprofloxacin has bactericidal and bacteriostatic characteristics due to the interference with the DNA-gyrase, an enzyme bacteria use for the synthesis of DNA. This leads to a halt in the passage of vital information from the bacterial chromosomes, which causes a rupture in the metabolism of the bacteria.

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In vitro ciprofloxacin acts very strongly against almost all gram-negative micro-organisms, including *Pseudomonas aeruginosa*. It is also active against gram-positive bacteria, like Staphylococci and Streptococci. Anaerobic bacteria generally are less susceptible.

Resistance to ciprofloxacin only seldom occurs. A bacterial resistance caused by plasmides does not seem to occur with antibiotics of the fluoroquinolone class.
Ciprofloxacin has already proven to possess the biggest antibacterial activity of all quinolones, though parallel-resistance exists within this group of gyrase inhibitors.

Thanks to its unique action there is no cross-resistance between ciprofloxacin and other antibacterial components chemically differing in structure like betalactamines, aminoglycosides, tetracyclines, macrolids, peptide antibiotics, nor with sulphonamides, trimethoprim, nitrofuran and their derivatives.

5.2 Pharmacokinetic properties

Following topical administration in the eye ciprofloxacin is also systemically absorbed. The plasma levels of volunteers varied from non-measurable to 4.7 ng/ml (about 450 times less than levels observed after oral administration of only 250 mg).

Following topical administration in the ear the systemic absorption is neglible. The plasma levels were not measurable 1 hour after instillation into the ear, even when the eardrum was perforated.

5.3 Preclinical safety data

No data provided.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride 0.06 mg – Disodium edetate – Mannitol – Sodium acetate – Acetic acid – Concentrated hydrochloric acid and/or Sodium hydroxide (to adjust pH) – Purified water to 1 ml.

6.2 Incompatibilities

Incompatible with alkaline solutions. (bases)

6.3 Shelf life

Unopened: 24 months.
See expiry date on the packaging after the sign "EXP" (month/year).
Discard this medicine 4 weeks after opening of the flask.

6.4 Special precautions for storage

Store at room temperature (15-25°C).

6.5 Nature and contents of container

5 ml DROP-TAINER®.

6.6 Instruction for use [and][,] handling [and disposal]

No special requirements.

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