CILOXAN®

Sterile Ophthalmic and Otic Solution
(Ciprofloxacin 0.3%)

1. NAME OF THE MEDICINAL PRODUCT

CILOXAN® Sterile Ophthalmic and Otic Solution 0.3%.
CILOXAN (ciprofloxacin hydrochloride solution), 0.3% as base

2. QUALITATIVE AND QUANTITAVE COMPOSITION

1 ml of CILOXAN 0.3% Sterile Ophthalmic and Otic Solution contains 3.5 mg ciprofloxacin hydrochloride equivalent to 3 mg base

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye/Ear drops, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CILOXAN Eye/Ear drops Solution is indicated for the treatment of corneal ulcers and superficial infections of the eye and its adnexa, caused by strains presumed or reported susceptible to Ciprofloxacin, in particular *Pseudomonas aeruginosa* and other Gram-negative bacteria resistant to usual treatments.
CILOXAN Eye/Ear drops Solution is also indicated for localized or diffuse otitis externa accompanied by a strong inflammatory reaction and of which the strains are susceptible to Ciprofloxacin.

4.2 Posology and method of administration

Corneal ulcers

CILOXAN Eye/Ear drops Solution must be administered at the following intervals, even during night time:
On the 1st day: instill 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: instill 2 drops into the affected eye hourly.
On the 3rd through the 14th day, place 2 drops into the affected eye 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.

Superficial bacterial infections of the eye and adnexa

For the first 2 days instill 1 or 2 drops into the conjunctival sac of the infected eye(s) every 2 hours during daytime. Then 1 or 2 drops every 4 hours during daytime until the bacterial infection is resolved.

Otic use

First thoroughly clean the external auditory duct. It is more agreeable to administer the solution at room temperature, and better still at body temperature, because in this way vestibular stimulation is avoided. Apply the product dropwise in the external ear duct; the dosage is 3 to 4 drops, 2 to 4 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 5 to 10 minutes. After local cleaning, an impregnated tent of gauze or a hydrophylic plug of cotton can also be inserted in the ear duct, and is generally left in place for 1 to 2 days, but should be impregnated to saturation with the product 2 times per day. In general, the duration of the treatment does not exceed 5 to 10 days. In some cases, the treatment can be prolonged, but, in such cases, it is advisable that the sensitivity of the local flora be demonstrated. As with all antibacterial preparations, prolonged use may lead to overgrowth with non-susceptible microorganisms or fungi.

4.3 Contraindications

Hypersensitivity to any component of this medication. The use of CILOXAN Eye/Ear drops Solution is also contraindicated in patients with hypersensitivity to other quinolones.

4.4 Special Warnings and precautions for use

- 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. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.
- Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.
- As with all antibacterial preparations, prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates (ophthalmologic use), the patient should be examined with slit lamp biomicroscopy.
- 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/Ear drops solution should be discontinued at the first sign of tendon inflammation.
- In patients with corneal ulcer and frequent administration of the drug white precipitates have been observed which resolved after continuous application of CILOXAN Eye/Ear drops solution for ocular use only. The precipitate does not preclude continued use of CILOXAN Eye/Ear drops solution, nor does it adversely affect the clinical course of the recovery process.

Contact Lenses

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 Eye/Ear drops solution. CILOXAN Eye/Ear drops solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of CILOXAN Eye/Ear drops solution and wait at least 15 minutes before reinsertion.

CILOXAN Eye/Ear drops solution contains benzalkonium chloride which may be irritant and may cause skin reactions for otic use only.

For use in children
Safety and efficacy in pediatric patients below age of 1 have not been established. Although ciprofloxacin and other quinolones cause anthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any anthropathy, and there is no evidence that ophthalmic dosage form has any effect on the weight bearing joints.

4.5 Interactions with other medicinal products and other forms of interaction

- Specific drug interaction studies have not been conducted with ophthalmic Ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, to interfere with the metabolism of caffeine, and to enhance the effect of the oral anticoagulant, warfarin, and its derivatives. Transient elevations in serum creatinine have been reported in patients receiving cyclosporine concomitantly with systemic Ciprofloxacin.
- Given the low systemic concentration of ciprofloxacin following topical ocular or otic administration of the product, drug interactions are unlikely to occur.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of CILOXAN Eye/Ear drops solution in pregnant women. Animal studies with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity. CILOXAN Eye/Ear drops solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

Ciprofloxacin is excreted in human milk after its oral administration. It is unknown whether ciprofloxacin is excreted to human milk following topical ocular or otic administration. A risk to the suckling child cannot be excluded. Therefore, caution should be exercised when CILOXAN Eye/Ear drops solution is administered to nursing mothers.

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

Ocular use:
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon administration, the patient must wait until the vision clears before driving or using machinery.

Otic use:
There are no data on the effect of CILOXAN Eye/Ear drops solution on the ability to drive and use machine.

4.8 Undesirable Effects

The following adverse reactions have been reported during clinical trials with CILOXAN Eye/Ear drops solution and 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.

Ocular Use:
The following undesirable effects were reported in association with the ophthalmic use of CILOXAN Eye/Ear drops solution and Eye Ointment:

System Organ Classification	**Adverse reactions** *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

Otic Use:
The following undesirable effects were reported in association with the otic use of CILOXAN Eye/Ear drops solution:

System Organ Classification	**Adverse reactions** *MedDRA Preferred Term (v.15.1)*
Nervous system disorders	*Uncommon:* headache
Ear and labyrinth disorders	*Uncommon:* ear pain, ear congestion, otorrhoea, ear pruritus
Skin and subcutaneous tissue disorders	*Uncommon*: dermatitis
General disorders and administration site conditions	*Uncommon*: pyrexia

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

Ocular Use:

System Organ Classification	**Adverse reactions** *MedDRA Preferred Term (v.15.1)*
Musculoskeletal and connective tissue disorders	tendon disorder

Otic Use:

System Organ Classification	**Adverse reactions** *MedDRA Preferred Term (v.15.1)*
Ear and labyrinth disorders	tinnitus

4.9 Overdose
Due to the characteristics of this preparation no toxic effects are to be expected with an ocular or otic overdose of this product, nor in the event of accidental ingestion of the contents of one bottle/tube.
In case of topical overdose of CILOXAN Eye/Ear drops solution, eliminate the overdose by tap water.

5. PHARMACOLOGICAL PROPERTIES

Microbiological properties
CILOXAN Eye/Ear drops Solution contains Ciprofloxacin Hydrochloride and is especially prepared for ophthalmic and otic use. This solution is particularly suitable for the treatment of disorders whereby a local, non- systemic effect is desired.
Ciprofloxacin has cidal and inhibitory activities against bacteria which result from an interference with the DNA gyrase, an enzyme needed by the bacterium for the synthesis of DNA. Thus the vital information from the bacterial chromosomes cannot be transcribed any longer which causes a break-down of the bacterial metabolism.
Ciprofloxacin has a very high *in vitro* activity against almost all Gram-negative microorganisms including *Pseudomonas aeruginosa*. It is also effective against Gram-positive bacteria, such as Staphylococci and Streptococci. Anaerobes are in general less susceptible.
Resistance development against Ciprofloxacin occurs infrequently.
A plasmid-mediated bacterial resistance does not appear to occur with the fluoroquinolone class of antibiotics. Ciprofloxacin has been shown to possess the greatest antibacterial activity of all quinolones; however, parallel resistance is seen with this group of gyrase inhibitors.

Due to its special mode of action, there is no cross-over resistancy between Ciprofloxacin and other anti-bacterial compounds with different chemical structures, such as beta-lactam antibiotics, aminoglycosides, tetracyclines, macrolide and peptide antibiotics as well as sulfonamides, trimethoprim and nitrofuran derivatives.

Pharmacokinetic properties
After topical ocular administration Ciprofloxacin is also absorbed systemically. Plasma levels in volunteers ranged from nonquantifiable to 4.7 ng/ml (some 450-fold less than levels observed following simple 250 mg oral administration).
Following topical administration in the ear, the systemic absorption can be considered as negligible. The plasma levels were not measurable 1 hour after administration of the drops in the ear, even if the eardrum was perforated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Excipients: Inactive ingredients are disodium edetate, mannitol, glacial acetic acid, sodium acetate trihydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment, and purified water
Preservative: Benzalkonium chloride 0.006% (0.06 mg/ml)

6.2 Incompatibilities
Alkaline solutions (bases).

6.3 Shelf life
Unopened: see expiry date on the package after the sign "EXP" (month/year). Discard 4 weeks after opening.

6.4 Special precautions for Storage
Store at or below 30°C. Protect from light. Keep out of reach of children.
Do not refrigerate or freeze.

6.5 Nature and contents of container
5 ml DROPTAINER® dispenser.

6.6 Manufacturer
See folding box

(Information Issued: Feb 2013.SINv1)

Novartis Pharma AG, Basel, Switzerland