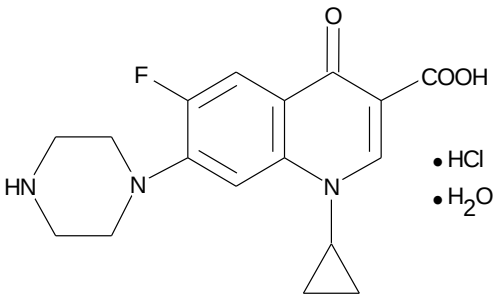
PRODUCT INFORMATION

CILOXAN* (ciprofloxacin) 0.3% Ear Drops

NAME OF THE MEDICINE

CILOXAN Ear Drops contain ciprofloxacin hydrochloride (equivalent to 3 mg/mL ciprofloxacin base). The chemical structure of ciprofloxacin hydrochloride is represented as:



Empirical formula: $C_{17}H_{18}FN_30_3.HCl.H_20$

Molecular weight: 385.8

Chemical name: monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid

CAS Registry Number: 86393-32-0

DESCRIPTION

Ciprofloxacin, a faint to light yellow crystalline powder which is soluble in water, is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative otic pathogens.

CILOXAN Ear Drops is a sterile, multiple-dose product, for topical otic use. The pH of CILOXAN Ear Drops is approximately 4.5 and the osmolality is approximately 300 mOsm.

CILOXAN Ear Drops also contain sodium acetate, acetic acid, mannitol, disodium edetate, hydrochloric acid and/or sodium hydroxide (to adjust pH), purified water and benzalkonium chloride (0.06 mg/mL) as preservative.

PHARMACOLOGY

Pharmacokinetics

After instillation to the ear canal, ciprofloxacin is concentrated directly at the site of infection (approximately 3000 µg/mL in the middle ear).

Published studies in paediatric and adult patients with a tympanic perforation (artificial or natural), showed minimal systemic absorption of ciprofloxacin following ototopical administration. Following tympanostomy tube insertion in paediatric patients who received a single bilateral topical otic dose of an ear drop containing ciprofloxacin 0.3%, plasma concentrations of ciprofloxacin (up to 6 hours following administration) were quantifiable in only 2 of 9 patients. The mean peak plasma concentrations of ciprofloxacin was 1.39 ng/mL Peak plasma concentrations ranged from 0.54 ng/mL to 3.45 ng/mL and were on average approximately 0.1% of peak plasma concentrations achieved with an oral dose of 250 mg. Peak plasma concentrations were observed within 15 minutes to 2 hours post dose application.

Microbiology

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms.

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in chronic suppurative otitis media (CSOM):

Gram-Positive:

- *Staphylococcus* species, including *Staphylococcus aureus* and *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*
- β-hemolytic *Streptococcus*

Gram-Negative:

- *Haemophilus influenzae*
- *Pseudomonas* species including *Pseudomonas aeruginosa*
- *Serratia* species
- *Proteus* species, including *Proteus mirabilis*
- *Klebsiella* species including *Klebsiella aerogenes*
- *Enterobacteriaceae* species, including *Escherichia coli.*

Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation). The plasmid-mediated bacterial resistance does not appear to occur with the fluoroquinolone class of antibiotics, however, parallel resistance is seen with this group of gyrase inhibitors.

Due to its special mode of action there is no cross-over resistance between ciprofloxacin and other antibacterial compounds with different chemical structures, such as β-lactam antibiotics, aminoglycosides, tetracyclines, macrolide and peptide antibiotics as well as sulfonamides, trimethoprim and nitrofuran derivatives, therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

Co-selection of resistance to β-lactam antibiotics and tetracyclines via over expression of multi-drug resistance efflux has been shown in ciprofloxacin-resistant *Staphylcoccus aureus* strains.

Toxicological Properties

An ototoxic study was conducted in which guinea pigs received 0.3% ciprofloxacin solution, twice a day, directly onto the round window membrane. Auditory Brainstem Response findings following two and four weeks of treatment revealed no significant differences in intraaural threshold response (treated vs. untreated ear) or in absolute threshold at any of the frequencies tested (2,8 and 16 kHz). Histopathologic evaluation of the cochlear hair cells demonstrated that the ciprofloxacin 0.3%, and saline control groups had hair cell loss within the normal range for guinea pigs. Profound hair cell loss, corresponding with loss of auditory function, was observed in the neomycin group.

CLINICAL TRIALS

Based on a review of 24 published studies (n= 1210) ciprofloxacin solution has been demonstrated to be safe and effective in the treatment of CSOM. The pivotal study was a double-blind, randomised controlled trial in Australian Aboriginal and Torres Strait Islander children (n=111) with CSOM, from 1 to 14 years and compared the effectiveness of ototopical ciprofloxacin 0.3% (CIP) with framycetin (0.5%), gramicidin, dexamethasone (FGD) eardrops when dosed 5 drops twice daily for 9 days (Couzos *et al.*,). Regular aural toilet (povidone-iodine (0.5%) was also employed. The primary endpoint was resolution of otorrhoea (clinical cure).

Clinical cure was significantly higher in patients treated with CIP (76.4%; p= 0.009, absolute difference of 24.6% [95% CI, 15.8%-33.4%]) compared with patients treated with FGD (51.8%).

No change in hearing or tympanic membrane healing was evident in the short follow-up period of 10-21 days after treatment in this study. Longer term data is needed to determine the effect of topical antibiotic therapy on tympanic membrane healing and the level of healing impairment.

The safety profile from these published studies support that the otic administration of ciprofloxacin 0.3% is well tolerated. There have been no reports of ototoxicity associated with ciprofloxacin 0.3% ear drops.

INDICATIONS

Treatment of chronic suppurative otitis media (CSOM) when caused by organisms susceptible to ciprofloxacin in adults and children 1 month or older.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or any other component of the medication. A history of hypersensitivity to other quinolones, including nalidixic acid, may also contraindicate the topical use of ciprofloxacin.

PRECAUTIONS

FOR TOPICAL USE ONLY - NOT FOR INJECTION

FOR OTIC USE ONLY

CILOXAN Ear Drops should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic 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 anaphylactic reactions require immediate emergency treatment with adrenaline and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically required.

Moderate to severe phototoxicity manifested by an exaggerated sunburn reaction has been observed in some patients who were exposed to direct sunlight while receiving some members of the quinolone class of drugs, including oral ciprofloxacin. Excessive sunlight should be avoided.

General

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection has not improved after 9 days of treatment, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body or a tumour.

Safety and efficacy of ciprofloxacin ear drops have not been established for treatment periods longer than 14 days.

The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

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 0.3% Ear Drops should be discontinued at the first sign of tendon inflammation.

CILOXAN 0.3% Ear Drops contain benzalkonium chloride which may be an irritant and cause skin reactions.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; based on body surface area 3-4 times the maximal recommended human oral dose of 1500 mg/day based on body surface area) and rats (oral doses up to 241 mg/kg/day and 328 mg/kg/day in males and females, respectively; based on body surface area 1-2 times the maximal recommended human oral dose of 1500mg/day) showed no evidence of ciprofloxacin – induced carcinogenicity.

Genotoxicity

In a battery of genotoxicity assays, ciprofloxacin was positive in the mouse lymphoma assay and the rat hepatocyte DNA repair assay *in vitro*, but negative in bacterial gene mutation assays, in assays for chromosomal damage *in vitro* and *in vivo*, in a cell transformation *in vitro*, and in the rat hepatocyte DNA repair assay *in vivo*.

Effects on fertility

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

Studies performed in rats and mice at oral doses of ciprofloxacin up to 100 mg/kg/day (based on body surface area 0.6 and 0.3 times, respectively, the maximal recommended daily human oral dose) revealed no evidence of impairment of fertility due to ciprofloxacin.

Use in Pregnancy

Category B3

Reproduction studies in rats and mice at oral doses of up to 100 mg/kg/day (based on body surface area 0.6 and 0.3 times, respectively, the maximal recommended human oral dose) and intravenous doses of up to 30mg/kg have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally, based on body surface area 0.4 and 1.2 times, respectively, the maximal recommended human oral dose) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration at doses up to 20 mg/kg, no maternal toxicity was produced and no embryo-toxicity or teratogenicity was observed at either dose. In rabbits, intravenous administration of doses up to 20mg/kg did not elicit maternal toxicity, embryo-toxicity or teratogenicity.

There are no adequate and well controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals. As a precautionary measure, it is preferable to avoid the use of CILOXAN during pregnancy. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

Ciprofloxacin is excreted in human milk with systemic use. It is not known whether topically applied ciprofloxacin is excreted in human milk. Since ciprofloxacin causes arthtopathy in immature animals, caution should be exercised when ciprofloxacin is administered to a nursing mother.

Paediatric Use

Efficacy and safety in children less than one year old have not been assessed. Oral administration of ciprofloxacin and other quinolones has been shown to cause arthropathy in immature animals of most species tested. However, there is no evidence that otic dosing has any effect on the weight-bearing joints. Caution should be exercised when ciprofloxacin is administered to very young children. In otic use, frequent medical monitoring is required in order to be able to determine in a timely manner the possible necessity of other therapeutic measures.

Hepatic/Renal Impairment

Safety and effectiveness in patients with hepatic or renal impairment have not been established.

Effects on Ability to Drive and Use Machines

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

INTERACTIONS WITH OTHER MEDICINES

Specific drug interaction studies have not been conducted with otic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant warfarin and its derivatives and have been associated with transient elevations in serum creatinine in patients receiving cyclosporin concomitantly.

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

ADVERSE EFFECTS

No serious adverse effects have been reported in published studies when ciprofloxacin ear drops have been used ototopically within the recommended dosage. Following otic administration, the following adverse events have been reported the most frequently (≥ 1%): Ear and Labyrinth Disorders: mild local intolerance, ear pain, ear discomfort (stinging), ear pruritus, ear infection (fungal; otomycosis).

Nervous System Disorders: dysgeusia (bitter taste), transient dizziness, vertigo, headache (cephalea).

Overall CILOXAN Ear Drops is well tolerated.

Post-marketing Events

The following adverse reactions are classified according to the following convention: very common, common, uncommon, rare, very rare, or not known (cannot be estimated from the available data), according to system organ classes. Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience.

Nervous system disorders:

Uncommon (> 0.1% to ≤ 1%): crying, headache.

Ear and labyrinth disorders:

Uncommon (> 0.1% to ≤ 1%): ear pain, ear congestion, otorrhoea, ear pruritis
Not Known: tinnitus.

Skin and subcutaneous tissue disorders:

Uncommon (> 0.1% to ≤ 1%): dermatitis.

General disorders and administration site conditions:

Uncommon (> 0.1% to ≤ 1%): pyrexia.

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

In otic use the ingredients rarely are sensitizing. However as with any substance that is applied to the skin, an allergic reaction to any of the ingredients of the preparation can always occur.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, 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.

Ruptures of the shoulder, hand, Achilles, 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 these ruptures may be increased in patients receiving corticosteroids, especially 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 CILOXAN and musculoskeletal and connective tissue adverse reactions.

DOSAGE AND ADMINISTRATION

Chronic suppurative otitis media (adults and children 1 month or older). The recommended dosage is: five (5) drops into the affected ear canal(s) twice daily for 9 days.

If the solution is cold, it should be warmed by holding the bottle in the hand for one or two minutes before instillation, to avoid dizziness which may be associated with instillation of a cold solution into the ear.

Patients should be advised to avoid contamination of the dispensing tip.

OVERDOSAGE

A topical overdose of CILOXAN Ear Drops may be flushed from the ear(s) with warm tap water. Accidental oral ingestion of CILOXAN is not likely to be associated with toxicity. Treatment of any exposure if symptomatic and supportive.

POISONS SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

PRESENTATION

As a sterile otic solution 1 mL, 2.5 mL and 5 mL in plastic DROP-TAINER* dispensers.

Consumer Medicine Information is included with this product.

STORAGE

Store below 25°C. Do not refrigerate or freeze. Protect from light.

Discard container 4 weeks after opening.

NAME AND ADDRESS OF SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

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Macquarie Park NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOOD (THE ARTG)

Approved by TGA on 17 May 2006

DATE OF MOST RECENT AMENDMENT

26 July 2017

*a trademark of Novartis

Reference:

Couzos *et al*., Effectiveness of ototopical antibiotics for chronic suppurative otitis media in Aboriginal children: a community-based, multicentre, double-blind randomized controlled trial. MJA 2003; 179: 185-190.

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