CILODEX® Ear Drops Suspension

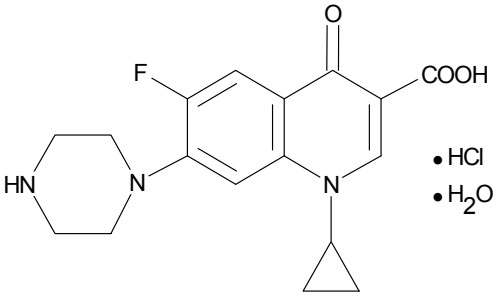
Ciprofloxacin hydrochloride 0.3% and dexamethasone 0.1%

Name of the Medicine

CILODEX Ear Drops is a sterile, stable, preserved suspension containing 0.3% w/v ciprofloxacin hydrochloride and 0.1% w/v dexamethasone.

Ciprofloxacin

Ciprofloxacin is a broad-spectrum antibacterial agent. The chemical structure of ciprofloxacin hydrochloride is represented as:



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

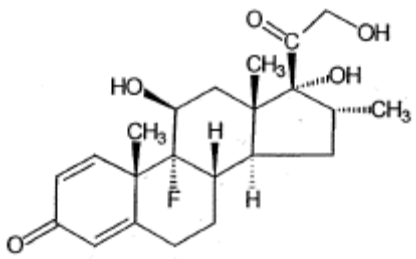
Molecular weight: 385.8

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

CAS Registry Number: 86393-32-0

Dexamethasone

Dexamethasone is an anti-inflammatory steroid. The chemical structure of dexamethasone is represented as:



Empirical formula: $C_{22}H_{29}FO_5$

Molecular weight: 392.47

Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

CAS Registry Number: 50-02-2

Description

CILODEX Ear Drops is a white to off-white suspension formulated as a sterile, multiple-dose product, for topical otic use.

Each 1 mL of CILODEX suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone. It also contains benzalkonium chloride (as a preservative), hydroxyethyl cellulose, sodium acetate, acetic acid, sodium chloride, disodium edentate, tyloxapol, boric acid, hydrochloride acid / sodium hydroxide (to adjust pH) and purified water

Pharmacology

Mechanism of Action

CILODEX contains the fluoroquinolone, ciprofloxacin. The cidal and inhibitory activity of ciprofloxacin against bacteria results 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 breakdown of the bacterial metabolism.

Ciprofloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative micro-organisms: anaerobes are less susceptible.

CILODEX also contains an anti-inflammatory agent, the corticosteroid dexamethasone.

The beneficial anti-inflammatory activity of dexamethasone is exerted by mechanisms, which are not completely understood. Dexamethasone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection (such as otorrhea in paediatric patients with acute otitis media with tympanostomy tubes).

Breakpoints

There are no official topical otic breakpoints for ciprofloxacin and although systemic breakpoints have been used, their relevance to topical otic therapy is doubtful. The systemic breakpoint used for this antibiotic is S $\leq$ 2mg/l, R $\geq$ 4mg/l.

Susceptibility to Ciprofloxacin

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections:

Acute Otitis Media with Tympanostomy Tubes (AOMT)

Commonly susceptible species (i.e., MIC50 of < 4 mg/l for at least 10 strains)

Aerobic Gram-positive micro-organisms:

Staphylococcus aureus, Staphylococcus epidermidis*, Streptococcus pneumoniae**

Aerobic Gram-negative micro-organisms:

Escherichia coli, Haemophilus influenzae, Moraxella catarrhalis*, Pseudomonas aeruginosa**

*denotes those species which have been satisfactorily demonstrated in clinical studies in at least 10 patients.

Acute Otitis Externa (AOE)

Commonly susceptible species (i.e., MIC50 of < 4 mg/l for at least 10 strains)

Aerobic Gram-positive micro-organisms:

Coryneform bacteria, *Enterococcus faecalis*, Staphylococcus aureus*, Staphylococcus capitis, Staphylococcus caprae*, Staphylococcus epidermidis*,*

Aerobic Gram-negative micro-organisms*:*

Acinetobacter genospecies 3, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens,*

*denotes those species which have been satisfactorily demonstrated in clinical studies in at least 10 patients.

The above information is based on microbiological surveillance studies performed at various sites in Europe and data obtained in the U.S.A. and Canadian clinical studies.

Pharmacokinetics

Ciprofloxacin

Following a single bilateral 4-drop per ear (8 drops per administration) dose of CILODEX in 25 paediatric patients, the mean plasma ciprofloxacin C_{max} was 1.33 ± 0.96 ng/mL. Thereafter, ciprofloxacin concentrations decreased and were not quantifiable (< 0.50 ng/mL) in 21 patients at 6 hours post-dose, indicating low systemic exposure. The mean ciprofloxacin C_{max} (1.33 ng/mL) was about 570 fold lower than the mean C_{max} of 760 ng/mL reported after a therapeutic 250 mg ciprofloxacin oral dose in adult subjects. The mean ciprofloxacin t½ was approximately 3 hours and was similar to that reported in adult subjects after oral administration.

Dexamethasone

Following a single bilateral 4 drops per ear (8 drops per administration) dose of CILODEX in 24 paediatric patients, the mean plasma dexamethasone C_{max} was 0.90 ± 1.04 ng/mL. Thereafter, dexamethasone concentrations decreased and were not quantifiable (< 0.05 ng/mL) in 10 patients at 6 hours post-dose, indicating low systemic exposure. The mean dexamethasone Cmax (0.90 ng/mL) was about 8.8 fold lower than the mean C_{max} of 7.9 ng/mL reported after a 0.5 mg oral dose of dexamethasone in adult subjects. The mean dexamethasone t½ was approximately 4 hours and was similar to that reported in adult subjects after oral administration.

The systemic exposure to ciprofloxacin and dexamethasone observed in clinical studies following topical otic administration of CILODEX represents the maximum in paediatric acute otitis media with tympanostomy tubes (AOMT) patients because of the presence of patent tympanostomy tubes without otorrhea. The systemic exposure to both drugs in acute otitis externa (AOE) patients following topical otic administration of CILODEX would not be expected to be as high as those seen in paediatric patients with tympanostomy tubes due to lower bioavailability of topical drugs through an intact tympanic membrane.

Toxicological properties

Clinical studies indicate that ciprofloxacin is non-ototoxic.

There is no evidence that the topical otic administration of CILODEX has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Guinea pigs dosed in the middle ear with CILODEX for one month exhibited no drug related structural or functional changes of the cochlear hair cells and no lesions in the ossicles.

Clinical Studies

CILODEX has been studied in patients from 6 months and older in acute otitits media with tympanostomy tubes and acute otitis externa. In two randomised, multicentre, controlled clinical trials, CILODEX was effective in treating acute otitis media with otorrhoea in tympanostomy patients. The clinical cures for CILODEX in the per protocol analyses were 91% and 86% compared to 80% for ciprofloxacin 3 mg/mL (CILOXAN) and 79% for ofloxacin 3 mg/mL (FLOXIN). Among the culture positive patients, clinical cures were 89% and 90% for CILODEX compared to 80% for ciprofloxacin 3 mg/mL (CILOXAN) and 79% ofloxacin 3 mg/mL (FLOXIN). Microbiological eradication rates for these same patients were 90% and 91% for CILODEX compared to 80% for ciprofloxacin 3 mg/mL (CILOXAN) and 82% for ofloxacin 3 mg/mL (FLOXIN). CILODEX had a 4 day median time to cessation of otorrhoea.

In two randomised, multicentre, controlled clinical trials, CILODEX was effective in treating acute otitis externa (AOE) patients. The clinical cures for CILODEX in the per protocol analyses were 94% and 87% compared to 86% for ciprofloxacin 3 mg/mL (CILOXAN) and 89% and 84%, respectively, for neomycin 3.5mg/ml+polymyxin B 10,000 IU/mL +

hydrocortisone 10 mg/mL (CORTISPORIN) otic suspension. Among the culture positive patients, clinical cures were 92% and 86% for CILODEX compared to 87% for ciprofloxacin 3 mg/mL (CILOXAN) and 89% and 84%, respectively, for neomycin 3.5mg/mL + polymyxin B 10,000 IU/mL+ hydrocortisone 10 mg/mL (CORTISPORIN) otic suspension. Microbiological eradication rates for these same patients were 92% and 86% for CILODEX compared to 87% for ciprofloxacin 3 mg/mL (CILOXAN) and 85% and 85%, respectively, for neomycin 3.5mg/ml+polymyxin B 10,000 IU/mL + hydrocortisone 10 mg/mL (CORTISPORIN) otic suspension. CILODEX had a 5 day median time to cessation of pain.

No clinically relevant changes in hearing function were observed in 69 paediatric patients (age 4 to 12 years) treated with CILODEX and tested for audiometric parameters.

Indications

CILODEX is indicated for the topical treatment of acute otitis media in patients with tympanostomy tubes and acute otitis externa in patients caused by strains of bacteria susceptible to ciprofloxacin.

Consideration should be given to official guidance on the appropriate use of antibiotic agents.

Contraindications

CILODEX is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, to dexamethasone or to any of the excipients in this medication.

Precautions

FOR TOPICAL USE ONLY

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.

As with other antibacterial preparations, use of this product may result in overgrowth of non-susceptible organisms, including yeast and fungi. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment.

In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angiooedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching. If an allergic reaction to CILODEX occurs, discontinue use of the drug. Serious acute hypersensitivity reactions to ciprofloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

Effects on Fertility

The effect of dexamethasone on fertility has not been investigated following short-term topical otic application. However topical dermal studies have shown effects on male sex organs following long-term use of dexamethasone doses much higher than those resulting from use of CILODEX.

Use in Pregnancy- Category B3

Teratogenic effects

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the foetus as a result of ciprofloxacin.

After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Since no animal reproduction studies or no adequate or well controlled studies in pregnant women have been conducted, CILODEX should not be used during pregnancy unless clearly necessary and only if the potential benefit justifies the potential risk to the foetus.

Women of child-bearing potential

There are no special recommendations for women of childbearing potential.

Use in Lactation

Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. It is not known whether topical administration to humans could result in sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised if CILODEX is administered during lactation. There are no special recommendations

Use in Children and Elderly

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

CILODEX has been shown to be safe and effective in paediatric patients and can be used at the same dose as in adults.

Renal & Hepatic Impairment

Hepatic or renal impairment (mild to moderate) does not alter the pharmacokinetics of ciprofloxacin or dexamethasone following systemic administration.

Following topical otic administration of CILODEX, small increases in ciprofloxacin and dexamethasone plasma concentrations may be observed in patients with severe renal or hepatic impairment. However, since systemic exposure to ciprofloxacin or dexamethasone is low after topical otic administration, any increase in systemic concentrations due to renal or hepatic dysfunction would still be well below plasma concentrations that are well tolerated in children or adults following oral or intravenous recommended doses.

Dose adjustment of CILODEX in patients with renal or hepatic dysfunction is not necessary.

Carcinogenicity and Mutagenicity

No long-term studies of CILODEX have been performed to evaluate carcinogenic potential.

Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone.

Genotoxicity

Dexamethasone has been shown to be genotoxic in several model systems while negative in others. The relevance of these findings for human clinical use is not known.

Drug Interactions

Specific drug-drug interaction studies were not conducted with CILODEX. Following topical otic administration of CILODEX in paediatric patients with patent tympanostomy tubes, low plasma concentrations were observed for ciprofloxacin (≥ 0.50 ng/mL in only 4 of 25 patients) and for dexamethasone (≥ 0.05 ng/mL in 14 of 24 patients) at 6 hours post dose. It is concluded that clinically relevant drug-drug pharmacokinetic interactions for ciprofloxacin or dexamethasone through protein binding, or involving P450 metabolism with concomitant medications, would be unlikely for both compounds following topical otic administration of CILODEX.

Oral administration of ciprofloxacin has been shown to inhibit cytochrome P450 CYP1A2 and CYP3A4 isozymes, and alter the metabolism of methylxanthine compounds (caffeine, theophylline). Following topical otic administration of CILODEX, ciprofloxacin plasma concentrations are low, and it is unlikely that an interaction involving P450 metabolism with concomitant medications would result in clinically relevant changes in plasma levels of methylxanthine compounds.

Adverse Effects

In clinical studies involving 969 patients, CILODEX was administered once or twice daily. This included 432 patients with otitis media with tympanostomy tubes and 537 patients with acute otitis externa. Approximately 6% of patients can be expected to experience treatment-related undesirable effects.

Acute otitis media in patients with tympanostomy tubes

No serious otic or systemic treatment-related undesirable effects were reported with CILODEX. The most frequently reported treatment-related undesirable effects were ear discomfort (2.8%) and ear pain (2.1%).

The following undesirable effects assessed as definitely, probably, or possibly related to treatment with CILODEX were reported during the clinical trials. Their incidence was either common (1.0% to 10.0%; maximum observed actual incidence of 2.8%) or uncommon (0.1% to less than 1.0%).

<u>Ear and Labyrinth Disorders:</u>

Common: ear discomfort, and ear pain

Uncommon: ear pruritus, tinnitus, and ear disorder

<u>Infections and Infestations:</u>

Uncommon: candidal infection

<u>Psychiatric Disorders:</u>

Uncommon: irritability, and crying

<u>Nervous System Disorders:</u>

Uncommon: dysgeusia, and dizziness

General Disorders and Administration Site Conditions:

Uncommon: medication residue, and migration of implant (tympanostomy tube blockage)

Acute otitis externa

No serious otic or systemic treatment-related undesirable effects were reported with CILODEX. The most frequently reported treatment-related undesirable effect was ear pruritus (1.5%).

The following undesirable effects assessed as definitely, probably, or possibly related to treatment with CILODEX were reported during the clinical trials. Their incidence was either common (1.0% to 10.0%; maximum observed actual incidence of 1.5%) or uncommon (0.1% to less than 1.0%).

Ear and Labyrinth Disorders

Common: ear pruritus

Uncommon: cerumen impaction, ear congestion, ear pain, ear discomfort, and hypoacusis

Infections and Infestations

Uncommon: otitis externa fungal

Nervous System Disorders

Uncommon: paraesthesia (tingling in ear)

Vascular Disorders

Uncommon: flushing

Skin and Subcutaneous Tissue Disorders

Uncommon: rash scaly, and rash

Dosage and Administration

Shake well before use. The suspension should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward, and then the drops should be instilled. Instil four drops in the affected ear(s) twice a day for 7 days. For patients with acute otitis media with tympanostomy tubes, the tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds.

Repeat, if necessary, for the opposite ear.

To prevent contamination of the dropper tip, care should be taken not to touch the auricle or the external ear canal, and surrounding areas, or other surfaces with the dropper tip of the bottle.

Overdosage

The limited holding capacity of the ear canal for topical otic products practically precludes any overdosing of CILODEX. No cases of overdose have been reported.

Poison Schedule of the Drug

Prescription Only Medicine.

Presentation

CILODEX Ear Drops will be packaged in 5 mL natural low density polyethylene (LDPE) DROP-TAINER® dispenser bottle fitted with natural LDPE dispensing plug and white polypropylene closure.

Storage

Shelf life

After opening: 4 weeks

Store below 25°C. Do not freeze. Protect from light. Discard four weeks after first opening.

Name and Address of Sponsor

Distributed in New Zealand by:

Alcon New Zealand Limited
c/o Pharmaco (NZ) Limited
4 Fisher Crescent
Mt Wellington Auckland

Date of Preparation

16 August 2010

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