**1. NAME OF THE MEDICINAL PRODUCT**

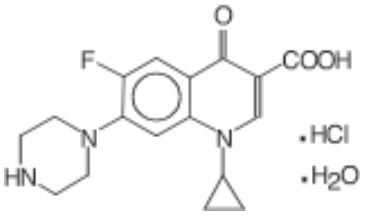
**CILODEX***
(ciprofloxacin 0.3% and dexamethasone 0.1%)
Sterile Otic Suspension

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

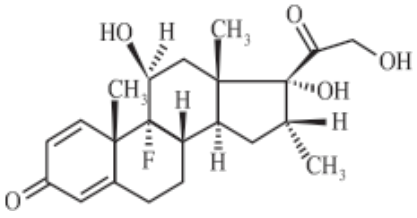
CILODEX* (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, dexamethasone, in a sterile, preserved suspension for otic use.

1 ml of suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone. 0.1 mg benzalkonium chloride as a preservative.

Ciprofloxacin, a fluoroquinolone is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and the structural formula is:




Dexamethasone, 9-fluoro-11(beta),17,21-trihydroxy-16(alpha)- methylpregna-1,4-diene-3,20-dione, is an anti-inflammatory corticosteroid. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:




For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**
Ear Drops, Suspension

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
CILODEX* Otic is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

**Acute Otitis Media** in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

**Pediatric Use:**
The safety and efficacy of CILODEX* Otic have been established in pediatric patients 6 months and older (937 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that would preclude use of this product.

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

**4.2 Posology and method of administration**

**Posology**

**Acute Otitis Media in pediatric patients with tympanostomy tubes:** The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (age 6 months and older) through tympanostomy tubes is: Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The solution 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 solution. The patient should lie with the affected ear upward, and then the drops should be instilled. 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. Discard unused portion after therapy is completed.

<u>Pediatric Use</u>
Safety and effectiveness in pediatric patients has been established as follows:

- 6 months and older (otic solution)

<u>Hepatic and renal impairment</u>
Dose adjustment in patients with renal or hepatic dysfunction is not necessary.
After cap is removed, if tamper evident snap collar is loose, remove before using product.

**4.3 CONTRAINDICATIONS**

- Hypersensitivity to the active substance, any of the excipients or other quinolones.
- Viral,fungal, and untreated parasitic otic infections.

**4.4 Special warnings and precautions for use**

**DO NOT TAKE BY MOUTH**

**FOR OTIC USE ONLY**
(This product is not approved for ophthalmic use.)

Warm the bottle in your hand for one to two minutes prior to use and shake well immedicately before using.

**NOT FOR INJECTION**
CILODEX* Otic 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. Serious acute hypersensitivity reactions may require immediate emergency treatment.

Avoid contaminating the tip with material from the ear, fingers, or other sources.

It is important that the infected ear(s) remain clean and dry. When bathing, avoid getting the infected ear(s) wet. Avoid swimming unless the doctor has instructed otherwise.

If rash or allergic reaction occurs, discontinue use immediately and contact your physician.
It is very important to use the ear drops for as long as the doctor has instructed, **even if the symptoms improve**.

- In patients receiving systemic 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, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria and itching. If an allergic reaction to ciprofloxacin occurs, discontinue use of product. Serious acute hypersensivity reactions require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

- Prolonged use of antibiotics may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

- If the infection is not improved after one week 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 tumor.

- 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 CILODEX* Otic should be discontinued at the first sign of tendon inflammation.

- Corticosteroids may reduce resistance to and aid in the establishment of non-susceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection.

- CILODEX* Otic contains benzalkonium chloride which may be irritant and may cause skin reactions.

**4.5 Interaction with other medicinal products and other forms of interaction**

No clinically relevant interactions have been described.

**4.6 Fertility, pregnancy and lactation**

Fertility

Studies have not been performed to evaluate the effect of topical administration of the combination of ciprofloxacin and dexamethasone on fertility. There is limited clinical data to evaluate the effect of ciprofloxacin and dexamethasone on male or female fertility. (See Section 5.3).

Pregnancy
Teratogenic Effects. Pregnancy Category C:
There are no or limited amount of data from the use of ciprofloxacin and dexamethasone in pregnant women. No animal reproduction studies and no adequate or well controlled studies in pregnant women have been conducted with the combination of ciprofloxacin and dexamethasone. Prolonged or repeated systemic corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of

hypoadrenalism.Ciprofloxacin was not teratogenic in mice, rats or rabbits. Studies in animals have shown reproductive toxicity after systemic administration of dexamethasone. The ocular administration of 0.1% dexamethasone also resulted in fetal anomalies in rabbits (See Section 5.3).

CILODEX* Otic is not recommended during pregnancy.

Breast-feeding

It is unknown whether Ciprofloxacin and Dexamethasone are excreted to human milk following topical ocular administration. Systemically administered ciprofloxacin has been found in human breast milk. No data is available on the passage of dexamethasone into human breast milk. However, it is not likely that the amount of ciprofloxacin and dexamethasone would be detectable in human milk or be capable of producing clinical effects in the infant following maternal use of the product. Nevertheless, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

**4.7 Effects on ability to drive and use machines**

There are no known effects of CILODEX* Otic on the ability to drive and use machines.

**4.8 Undesirable effects**

The following adverse reactions have been reported during clinical studies with

CILODEX* Otic 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) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

| System Organ Classification | MedDRA Preferred Term (v. 16.1) |
|---|---|
| Infections and infestations | *Uncommon:* candidiasis |
| Nervous system disorders | *Rare:* dizziness, headache |
| Ear and labyrinth disorders | *Common:* ear pain<br>*Uncommon:* otorrhoea, ear congestion, ear discomfort,<br>ear pruritus, ear infection fungal<br>*Rare:* hypoacusis, tinnitus, medication residue present |
| Gastrointestinal disorders | *Uncommon:* vomiting, dysgeusia |
| Skin and subcutaneous tissue disorders | *Uncommon:* skin exfoliation<br>*Rare:* rash erythematous |
| General disorders and administration site conditions | *Uncommon:* device occlusion, irritability |

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

| System Organ Classification | MedDRA Preferred Term (v. 16.1) |
|---|---|

| | |
|---|---|
| Ear and labyrinth disorders | auricular swelling |
| Immune system disorders | Hypersensitivity |

**4.9 Overdose**

Due to the characteristics of this preparation, no additional toxic effects are to be expected with an acute otic overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

**5. PHARMACOLOGICAL PROPERTIES**

***5.1. Pharmacodynamic Properties***

ATC Classification: *Pharmacotherapeutic group: OTOLOGICALS, Corticosteroids and anti-infectives in combination. ATC-Code: S02CA06*

Mechanisms of Action:

The *ear drops* contain the fluoroquinolone, Ciprofloxacin as the antibacterial agent. The bactericidal action of Ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

The *ear drops also contain the corticosteroid Dexamethasone.* The exact mechanism of action of Dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

Mechanism of Resistance:

In-vitro resistance to the antibacterial agent Ciprofloxacin can be acquired through a stepwise process by target site mutation in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between Ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance of efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to Ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported.

Breakpoints

Currently, minimal inhibitory concentration (MIC) breakpoints as established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) take into consideration drug concentrations achievable systemically following oral or intravenous administration of the antibiotic.

These Susceptible/Resistant (S/R in mg/L) breakpoints are used in every day clinical laboratory practice to predict clinical efficacy. However, when Ciprofloxacin is used by topical administration as in the otic or ophthalmic administration, higher concentrations could be achieved and the drug activity influenced by the physiochemical characteristics at this site of administration. There are no pharmacological data correlated with clinical outcome for Ciprofloxacin administered as a topical agent. As a result, the European Committee on Antimicrobial

Susceptibility Testing (EUCAST) suggests the following epidemiological cut-off values (ECOFF mg/L) derived from MIC distribution curves to indicate susceptibility to topical Ciprofloxacin.

EUCAST Recommended ECOFF Values for Ciprofloxacin

| Microorganisms | ECOFF (mg/L) |
|---|---|
| *Staphylococcus* species | 1 mg/L |
| *Streptococcus pneumoniae* | 2mg/L |
| *Haemophilus influenzae* | 0.06mg/L |
| *Moraxella catarrhalis* | 0.12mg/L |
| *Pseudomonas aeruginosa* | 0.5mg/L |

While EUCAST antibiotic breakpoints are not considered applicable for correlation to topically applied antibiotics, the following EUCAST breakpoints for ciprofloxacin are consistent for general use.

| Microorganisms | Susceptible (S) | Resistant (R) |
|---|---|---|
| *Staphylococcus* species | S ≤ 1mg/L | R > 1mg/L |
| *Streptococcus pneumoniae* | S ≤ 0.12mg/L | R > 2mg/L |
| *Haemophilus influenzae* | S ≤ 0.5mg/L | R > 0.5mg/L |
| *Moraxella catarrhalis* | S ≤ 0.5mg/L | R > 0.5mg/L |
| *Pseudomonas aeruginosa* | S ≤ 0.5mg/L | R > 1mg/L |

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. As 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.

**Acute Otitis Media with Tympanostomy Tubes (AOMT)**

| Commonly susceptible species |
|---|
| Aerobic Gram-positive micro-organisms:<br>*Staphylococcus aureus* (methicillin-susceptible)<br>*Streptococcus pneumoniae*<br>Aerobic Gram negative micro-organisms:<br>*Haemophilus influenzae*<br>*Moraxella catarrhalis*<br>*Pseudomonas aeruginosa* |
| Species for which acquired resistance may be a problem |
| Aerobic Gram-positive micro-organisms:<br>*Staphylococcus aureus* (methicillin-resistant) |

Pharmacodynamics

Dexamethasone is one of the most potent corticosteroids with a relative anti-inflammatory potency greater than prednisolone or hydrocortisone.

PK/PD relationship

A specific PK/PD relationship has not been established for Ciprofloxacin/Dexamethasone Suspension.

Pediatric Population

The safety and efficacy of Ciprofloxacin/Dexamethasone have not been studied in children. For information concerning posology, precautions, and warnings for pediatric subjects see Section 4.2 and 4.4, respectively.

**5.2. Pharmacokinetic Properties**

Ciprofloxacin Pharmacokinetics: Otic Use

Ciprofloxacin plasma levels following 4-drops/ear following tympanostomy surgery are low. In patients given 4 drop/ear the mean Ciprofloxacin Cmax was 1.55 + 0.71 ng/mL (range BLQ . 2.69 ng/mL) with a half-life which is similar to adults receiving oral administration.

Dexamethasone Pharmacokinetics: Otic Use
Dexamethasone plasma levels following 4-drops/ear following tympanostomy surgery are low. In patients given 4 drop/ear the mean Dexamethasone Cmax was 0.86 + 0.44 ng/mL (range 0.14 - 1.72 ng/mL).

***5.3. Preclinical Safety Data***

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical reproductive and developmental toxicity and exaggerated systemic pharmacology were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

**6. PHARMACEUTICAL PARTICULARS**
**6.1 List of excipients**

Boric acid
Sodium chloride
Hydroxyethyl cellulose
Tyloxapol
Acetic acid
Sodium acetate
Edetate disodium
Hydrochloric acid / sodium hydroxide
Purified water

**6.2 Incompatibilities**
Not applicable

**6.3 Shelf-life**
7.5mL: 24 months

**6.4 Special precautions for storage**

Store below 25°C. Avoid freezing. Protect from light.
Discard 4 weeks after first opening.
Discard unused portion after therapy is completed.

**6.5 Nature and content of container**

CILODEX* Otic is supplied as follows: 5 mL fill and 7.5 mL fill in a DROP-TAINER® system. The DROP-TAINER* system consists of a natural polyethylene bottle and natural plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.
Not all presentation are available locally.

**References:**

1. Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA, Ward A. Ciprofloxacin: A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1988;35:373-447.
2. Loew D, Schuster O, and Graul E. Dose-dependent pharmacokinetics of dexamethasone. Eur J Clin Pharmacol 1986;30:225-230.

**Alcon®**

Alcon Pharmaceuticals Ltd., Fribourg, Switzerland

Rx Only

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(Information Issued: Feb 2016.SIN)

**How should CILODEX* Otic be given?**

**1. Wash hands**

The person giving CILODEX* Otic should wash his/her hands with soap and water.

**2. Warm & shake bottle**

Hold the bottle of CILODEX* Otic in the hand for one or two minutes to warm the solution, then shake well.

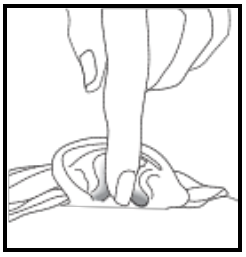
**3. Add drops**

The person receiving CILODEX* Otic should lie on his/her side with the infected ear up.

Patients should have 4 drops of CILODEX* Otic put into the infected ear. The tip of the bottle should not touch the fingers, or the ear, or any other surfaces.

**BE SURE TO FOLLOW INSTRUCTIONS BELOW FOR THE PATIENT'S SPECIFIC EAR INFECTION**

**4. For Patients with Middle Ear Infection with Tubes:**



While the person receiving CILODEX* Otic lies on his/her side, the person giving the drops should gently press the tragus (see diagram) 5 times in a pumping motion. This will allow the drops to pass through the tube in the eardrum and into the middle ear.

**5. Stay on side**

The person who received the ear drops should remain on his/her side for at least 60 seconds.

Repeat Steps 2-5 for the other ear if both ears are infected.