CILODEX®

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

1 Tradename(s)

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

2 Description and composition

Pharmaceutical form
Ear Drops, suspension

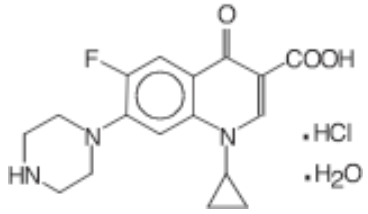
Active substances
Cilodex® Otic 1 ml of suspension contains 3.5 mg ciprofloxacin hydrochloride monohydrate (equivalent to 3mg of ciprofloxacin) and 1 mg dexamethasone.

Excipients

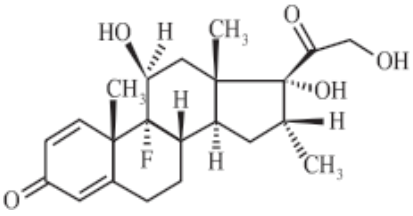
Excipient with known effect: 1 mL of the Ear drops, suspension contains 0.1 mg of benzalkonium chloride.

Other excipients: hydroxyethyl cellulose, sodium acetate (trihydrate), acetic acid, disodium edetate, sodium chloride, tyloxapol, boric acid, hydrochloric acid and / or sodium hydroxide (for pH adjustment) and purified water q.s.

Ciprofloxacin, a fluoroquinolone is available as the monohydrochloride monohydrate salt ofc1-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 antiinflammatory corticosteroid. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



3 Indications

Otic use
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 (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

4 Dosage regimen and administration

Dosage regimen

Acute Otitis Media in pediatric patients with tympanostomy tubes: 4 drops twice daily (BID) in the affected ear(s) for 7 days.

Special populations

Renal and hepatic impairment
When using Cilodex® Otic in patients with renal or hepatic impairment, dose adjustment is not necessary.

Pediatric patients
The safety and efficacy of Cilodex® Otic in pediatric patients below 6 months has not been established.

Method of administration

- For otic use only.
- The bottle must be shaken well before use.
- To avoid contamination, the dropper tip should not touch the ear or any other surface.
- The suspension should be warmed by holding the bottle in the hand for 1-2 minutes to avoid any unpleasant sensation 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. 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.

5 Contraindications

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

6 Warnings and precautions

DO NOT TAKE BY MOUTH

FOR OTIC USE ONLY

- This product is not approved for ophthalmic use. 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.
- 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 the 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.
- 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.
- There are no known effects of CILODEX® Otic on the ability to drive and use machines.
- 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.
- Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Special excipients

- Cilodex® Otic contains benzalkonium chloride which may be an irritant and may cause skin reactions.

7 Adverse drug reactions

Otic Use

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 7-1 Frequency of adverse drug reactions in clinical trials – otic use

System organ class	Adverse drug reactions	Frequency category
Infections and infestations	Candidiasis	Uncommon
Nervous system disorders	Dizziness, headache	Rare
Ear and labyrinth disorders	Ear pain	Common
	Otorrhoea, ear infection fungal, ear congestion, ear discomfort, ear pruritus	Uncommon
	Hypoacusis, tinnitus, medication residue present	Rare
Gastrointestinal disorders	Vomiting, dysgeusia	Uncommon
Skin and subcutaneous tissue disorders	Skin exfoliation	Uncommon
	Rash erythematous	Rare
General disorders and administration site conditions	Device occlusion, irritability	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions have been derived from post-marketing experience with Cilodex® Otic via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known) – otic use

System organ class	Adverse drug reactions
Ear and labyrinth disorders	Auricular swelling
Immune system disorders	Hypersensitivity

8 Interactions

No clinically relevant interactions have been identified.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are no adequate and well-controlled studies with Cilodex in pregnant women to inform a product-associated risk.

Prolonged or repeated systemic corticosteroid 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.

Animal reproduction studies have not been conducted with the combination of ciprofloxacin and dexamethasone.

Ciprofloxacin was not teratogenic in mice and rats. Studies in animals have shown reproductive toxicity after systemic administration of dexamethasone.

Cilodex should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

9.2 Lactation

Risk Summary

It is not known if ciprofloxacin and dexamethasone are transferred to human milk following topical otic administration.

Systemically administered ciprofloxacin has been found in human breast milk.
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.

No non-clinical studies have been conducted with dexamethasone in lactating animals.

However, a risk to the breast-fed 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.

9.3 Females and males of reproductive potential

Infertility

There are no data regarding the effects of topical otic administration of Cilodex on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility. Dexamethasone caused male reproductive toxicity at clinically relevant doses in rats. Ciprofloxacin did not impair fertility in rats.

10 Overdosage

Due to the characteristics of this preparation, no 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

ATC Classification: *Pharmacotherapeutic group:*

Otologicals; Corticosteroids and anti-infectives in combination. ATC-Code: S02CA06

Mechanism of action (MOA)

Cilodex contains the fluoroquinolone ciprofloxacin as the antibacterial agent. The cidal and inhibitory activity of ciprofloxacin involves inhibition of the α-subunit of bacterial enzyme, DNA gyrase (topoisomerase II) involved in gyrase-mediated DNA supercoiling and DNA synthesis. This process ultimately results in cell death. By targeting DNA gyrase, ciprofloxacin arrests bacterial cell growth and division by stabilizing the DNA-enzyme complex, which temporarily results in bacteriostasis. Subsequently, bacteria attempt but are unable to repair the DNA lesion. DNA ends from the ciprofloxacin-gyrase-DNA complex are eventually liberated creating lethal double-strand DNA breaks. Therefore, ciprofloxacin is bactericidal as well as bacteriostatic. The bactericidal activity of ciprofloxacin and other fluoroquinolones is concentration-dependent. Higher “kill rates” are achieved at peak concentrations.

Ciprofloxacin is active against a variety of aerobic Gram-positive and Gram-negative bacteria while anaerobic bacteria are less susceptible.
Dexamethasone: Cilodex *also contains the corticosteroid, dexamethasone.* The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

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

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.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

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 administration, higher concentrations could be achieved and the drug activity could be 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 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

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

EUCAST S/R Breakpoints for ciprofloxacin

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

Susceptibility to ciprofloxacin

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.

Commonly susceptible species

Aerobic Gram-positive micro-organisms:

- *Staphylococcus aureus* (methicillin-susceptible)
- *Streptococcus pneumoniae*

Aerobic Gram negative micro-organisms:

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Pseudomonas aeruginosa*

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms:

Staphylococcus aureus (methicillin-resistant)

Pharmacokinetics (PK)

Absorption

Topical otic administration

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

12 Clinical studies

Cilodex® Otic are well-established products.

13 Non-clinical safety data

Non-clinical data with ciprofloxacin and dexamethasone revealed no special hazard for humans based upon conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

14 Pharmaceutical information

Incompatibilities

Not applicable

Special precautions for storage

Ear drops: Store below 25ºC. Avoid freezing. Protect from light.

Discard 4 weeks after first opening.

Discard unused portion after therapy is completed.

Cilodex® Otic must be kept out of the reach and sight of children.

Instructions for use and handling

No special requirements.

Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer
See folding box.

(Information Issued: Mar 2022.SIN)

Novartis Pharma AG, Basel, Switzerland

How should CILODEX® Otic be given?

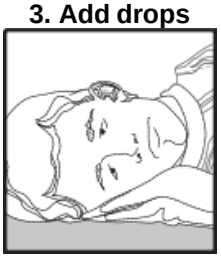
1. Wash hands

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

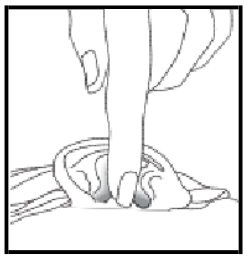


The person receiving CILODEX® Otic should lie on his/her side with the infected ear up.

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.