NOVARTIS

Cilodex Ear Drops (ciprofloxacin and dexamethasone)

3 mg ciprofloxacin and 1 mg dexamethasone, ear drops, suspension

Professional Information

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SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CILODEX Ear Drops (suspension)

2 QUALITIVE AND QUANTITIVE COMPOSITION

COMPOSITION:

1 ml of suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone

Preservative: Benzalkonium chloride 0.01 % (*m/v*)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

CILODEX is a white to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Use in adults including the elderly

Instil four drops in the affected ear(s) twice a day for 7 days.

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

Special populations

Use in children

CILODEX has been shown to be safe and effective in paediatric patients 6 months and older for the treatment of AOMT (acute otitis media with tympanostomy tubes) and 1 year of age and older for the treatment of AOE and can be used at the same dose as in adults.

Use in hepatic and renal impairment

Hepatic and 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 of 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.

Method of administration

Topical otic administration

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. Keep the bottle tightly closed when not in use.

Instructions for use and handling:

- 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.
- 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.

4.3 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.
- Viral and fungal otic infections and untreated parasitic otic infections.

4.4 Special warnings and precautions for use

- If otorrhoea persists after a full course of therapy, or if two or more episodes of otorrhoea

occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumour.

- Use of CILODEX 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, angioedema (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.
- Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.
- 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 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.
- For otic use only *(see section 4.2 Posology and method of administration).*

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

Paediatric population

Safety and efficacy of CILODEX have not been established in children younger than 6 months in acute otitis media in patients with tympanostomy tubes and in children younger than 1 year in acute otitis externa.

4.5 Interaction with other medicines and other forms of Interaction

- 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Corticosteroids are teratogenic 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.

Breastfeeding

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. Mothers using CILODEX should not breastfeed their infants.

Fertility

There is no clinical data to evaluate the effect of ciprofloxacin and dexamethasone as contained in CILODEX on male or female fertility.

4.7 Effects on ability to drive and use machines

CILODEX has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

In clinical studies involving 976 patients, CILODEX was administered once or twice daily. This included 439 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 adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (1/10), common (1/100 to <1/10), uncommon (1/1000 to <1/100), rare (1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Common	**Uncommon**	**Rare**
Infections and Infestations:		candidal infection	

Psychiatric disorders:		irritability	
Nervous system disorders:		paraesthesia (tingling in ears)	dizziness, headache
Ear and labyrinth disorders:	ear pain	otorrhoea, ear congestion, ear discomfort, ear pruritus, ear infection fungal	hypoacusis, tinnitus, medication residue present
Vascular disorders		flushing	
Metabolism and nutritional disorders:			hypoglycaemia, particularly in diabetic patients
Skin and subcutaneous tissue disorders		Skin exfoliation	rash erythematous
Gastrointestinal disorders:		vomiting, dysgeusia	
General disorders and administrative site conditions:		device occlusion (tympanostomy tube blockage), fatigue, crying	

Acute otitis externa:

No serious otic or systemic treatment-related undesirable effects were reported with CILODEX. The most frequent 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 %).

Description of selected adverse reactions

The most frequently reported adverse reactions reported in the 439 patients with acute otitis media with tympanostomy tubes were ear pain (2.5 %), ear discomfort (2.5 %), and dysgeusia (characterised as tasting the medicine) (1.1 %). Of these events, only 1 patient discontinued therapy with that being due to an occurrence of ear discomfort.

The most frequently reported adverse reaction reported in the 537 patients with acute otitis externa was ear pruritus (1.5 %). No patient discontinued therapy due to an occurrence of ear pruritus.

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, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching.

The development of secondary infections has occurred after the use of combinations containing corticosteroids or antimicrobials.

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 otic administration of ciprofloxacin as contained in CILODEX and these musculoskeletal and connective tissue adverse reactions.

Paediatric population

CILODEX has been shown to be safe in paediatric patients 6 months of age or older for the treatment of AOMT and 1 year of age or older for the treatment of AOE. The frequency, type and severity of adverse reactions in paediatric patients are expected to be the same as in adults.

Post-marketing adverse reactions

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

Body System	**Frequency: Not known**
Metabolism and nutritional disorders	Hyperglycaemia, hypoglycaemic coma
Ear and labyrinth disorders:	auricular swelling
General disorders and administrative site conditions:	hypersensitivity

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked

to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8 Undesirable effects*).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: OTOLOGICALS, Corticosteroids and anti-infectives in combination.

ATC-Code: S02CA06.

Mechanisms of action

The combination ear drop formulation contains the fluoroquinolone, ciprofloxacin. The bactericidal 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.

The combination ear drop formulation also contains an anti-inflammatory agent, the corticosteroid dexamethasone. The 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.

Susceptibility testing 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 ototopical administration, higher concentrations could be achieved in the ear and the drug activity influenced by the physiochemical characteristics at this site of administration. EUCAST breakpoints are not adequate for a topical antibiotic but these recommendations that follow are consistent for a general use.

EUCAST S/R Recommended Breakpoints for Ciprofloxacin (version 2.0-2012.01.01)

Microorganisms	**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 and Moraxella catarrhalis	S ≤ 0.5 mg/L	R ≥ 0.5 mg/L
Pseudomonas aeruginosa	S ≤ 0.5 mg/L	R ≥ 1 mg/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 microorganisms: *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 microorganisms:

Staphylococcus aureus (methicillin-resistant)

Acute Otitis Externa (AOE)

Commonly susceptible species
Aerobic Gram-positive microorganisms: *Staphylococcus aureus (methicillin- susceptible)* Aerobic Gram-negative microorganisms: *Pseudomonas aeruginosa*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms: *Staphylococcus aureus* (methicillin-resistant)

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.

5.2 Pharmacokinetic properties

Ciprofloxacin

Paediatric Population

Following a single bilateral 4-drop per ear (8 drops per administration) dose of the combination ear drop formulation 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 ~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 t1/2 was approximately 3 hours and was similar to that reported in adult subjects after oral administration.

Dexamethasone

Paediatric Population

Following a single bilateral 4-drop per ear (8 drops per administration) dose of the combination ear drop formulation 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 C_{max} (0.90 ng/ml) was ~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 t1/2 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 the combination ear drop formulation represents the maximum in paediatric AOMT patients because of the presence of patent tympanostomy tubes without otorrhea. The systemic exposure to both medicines in 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, hydroxyethyl cellulose, sodium acetate, acetic acid, sodium chloride, disodium edetate, tyloxapol, boric acid, hydrochloric acid / sodium hydroxide and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After opening

Discard four weeks after first opening.

6.4 Special precautions for storage

Store between 2 °C and 30 °C.

Do not freeze.

Keep bottle in the outer carton in order to protect from light. Discard four weeks after first opening.

Store in the original package/container.

6.5 Nature and contents of container

Colourless 5 ml low density polyethylene plastic bottle and plug.

White polypropylene closure.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

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Waterfall City

Jukskei view

2090

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF TEXT

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