SCHEDULING STATUS 4

PROPRIETARY NAME AND DOSAGE FORM
CILODEX Ear drops (suspension).

COMPOSITION:
1 ml of suspension contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone preserved with benzalkonium chloride 0.01 % (m/v).
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.

PHARMACOLOGICAL CLASSIFICATION
16.2 Aural preparations
ATC Classification
Pharmacotherapeutic group: Otological anti-infectives.
ATC code: S02A A

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Mechanisms of action
The combination ear drop formulation 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.
The combination ear drop formulation 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.
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.
Acute Otitis Media with Tympanotomy Tubes (AOMT)
Commonly susceptible species (i.e. resistance < 10 % or an MIC_{50} 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:
*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. resistance < 10 % or an MIC_{50} of < 4 mg/l for at least 10 strains)
Aerobic Gram-positive micro-organisms:
*Enterococcus faecalis**
*Staphylococcus aureus**
*Staphylococcus caprae**
*Staphylococcus epidermidis**
Aerobic Gram-negative micro-organisms:
*Pseudomonas aeruginosa**
Pharmacokinetic properties
Ciprofloxacin

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 $t_{1/2}$ was approximately 3 hours and was similar to that reported in adult subjects after oral administration.

Dexamethasone

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 $t_{1/2}$ 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 tympanotomy tubes without otorrhea. The systemic exposure to both drugs in AOE patients following topical otic administration of CILODEX would not be expected to be as high as those seen in paediatric patients with tympanotomy tubes due to lower bioavailability of topical drugs through an intact tympanic membrane.

INDICATIONS

CILODEX is indicated for the topical treatment of acute otitis media in patients with tympanotomy 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.

CONTRA-INDICATIONS

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.

WARNINGS

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.

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, 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 ability to drive and use machines

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

INTERACTIONS

Interaction with other medicinal products 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 tympanotomy 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.

PREGNANCY AND LACTATION

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.

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.

DOSAGE AND DIRECTIONS FOR USE

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.

Use in children

CILODEX has been shown to be safe and effective in paediatric patients 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

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 tympanotomy 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

In clinical studies involving 969 patients, CILODEX was administered once or twice daily. This included 432 patients with otitis media with tympanotomy 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 tympanotomy 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 %).

Infections and infestations

Uncommon: candidal infection.

Psychiatric disorders

Uncommon: irritability and crying.

Nervous system disorders

Uncommon: dysgeusia and dizziness

Ear and labyrinth disorders

Common: ear discomfort and ear pain.

Uncommon: ear pruritus, tinnitus and ear disorder.

General disorders and administration site conditions

Uncommon: medication residue and migration of implant (tympanotomy tube blockage).

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 %).

Infections and infestations
Uncommon: otitis externa fungal.

Nervous system disorders
Uncommon: paraesthesia (tingling in ear).

Ear and labyrinth disorders
Common: ear pruritus
Uncommon: cerumen impaction, ear congestion, ear pain, ear discomfort and hypoacusis.

Vascular disorders
Uncommon: flushing.

Skin and subcutaneous tissue disorders
Uncommon: rash scaly and rash.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

CILODEX is a white to off-white suspension.

PRESENTATION

Colourless 5 ml low density polyethylene DROP-TAINER bottle and plug. White polypropylene closure.

STORAGE INSTRUCTIONS

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.
Keep out of reach of children.

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