PROFESSIONAL INFORMATION LEAFLET: XINDEX® EAR DROPS

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

XINDEX Ear drops (suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 3 mg ciprofloxacin (as hydrochloride) and 1 mg dexamethasone.

Preservative: Benzalkonium chloride 0,01 % *m/v*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops, suspension (sterile).

Off-white, homogenous suspension, free of foreign particles in suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Organisms known to be susceptible to ciprofloxacin:

Acute Otitis Media with Tympanotomy Tubes (AOMT)

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

Aerobic Gram-positive micro-organisms:

*Staphylococcus aureus** (methicillin-susceptible)

*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 MIC50 of < 4 mg/l for at least 10 strains)

Aerobic Gram-positive micro-organisms:

*Enterococcus faecalis**

*Staphylococcus aureus** (methicillin-susceptible)

*Staphylococcus caprae**

*Staphylococcus epidermidis**

Aerobic Gram-negative micro-organisms:

*Pseudomonas aeruginosa**

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

4.2 Posology and method of administration

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:

XINDEX has been shown to be safe and effective in paediatric patients and can be used at the same dose as in adults. See section 4.4

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 XINDEX, 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 XINDEX in patients with renal or hepatic dysfunction is not necessary.

Method of administration:

For otic use only.

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.

4.3 Contraindications
Hypersensitivity to ciprofloxacin, to other quinolones, to dexamethasone or to any of the excipients of XINDEX listed in section 6.1.
Viral (i.e. varicella, herpes simplex) and fungal otic infections.

4.4 Special warnings and precautions for use
Prescribers should adhere to the principles of antibiotic stewardship.
This medicinal product is for otic use only, not for ophthalmic use, inhalation or injection.

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 XINDEX may result in overgrowth of non-susceptible organisms, including bacterial strains, yeast and fungi. If superinfection occurs, discontinue use and appropriate therapy should be initiated. 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 occurs, discontinue use of XINDEX. 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.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients, in patients treated currently with corticosteroids 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 and these musculoskeletal and connective tissue adverse reactions. Treatment with XINDEX should be discontinued at the first sign of tendon inflammation.

Corticosteroids may reduce resistance to, and aid in, the establishment of bacterial, viral, or fungal infections and mask the clinical signs of an infection, preventing recognition of ineffectiveness of the antibiotic, or may suppress hypersensitivity reactions to substances in the product.

Visual disturbance:
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.

XINDEX contains 0,10 mg benzalkonium chloride in each ml. Benzalkonium chloride may irritate the skin and cause local skin reactions.

Paediatric population
Safety and efficacy of ciprofloxacin/dexamethasone as in XINDEX 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. Under exceptional circumstances, ciprofloxacin/dexamethasone treatment could be used in this sub-paediatric population after a very careful benefit-risk evaluation by the medical practitioner taking into account that although there are no known safety concerns or differences in disease process to preclude use in these children, clinical experience is insufficient in these specific subgroups of paediatric population.

4.5 Interaction with other medicines and other forms of interaction
No specific drug-drug interaction studies have been performed.
Following topical otic administration of ciprofloxacin/dexamethasone as in XINDEX ear drops 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 ciprofloxacin/dexamethasone as in XINDEX ear drops.

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 ciprofloxacin/dexamethasone ear drops, 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

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, XINDEX 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. Caution should be exercised if XINDEX is administered during lactation.

Fertility

No human data on the effect of ciprofloxacin/dexamethasone on fertility are available (see also section 5.3). Topical dermal studies in animals have shown effects on male sex organs following long-term use of dexamethasone at high doses. Reproduction studies performed in rats and mice at doses up to six-times the usual daily human oral dose revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines

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

XINDEX may cause blurred vision or other visual disturbances which may affect the ability to drive and use machines. The patients should be advised not to drive or use machines until they know how treatment with XINDEX affects them.

4.8 Undesirable effects

The following adverse reactions have been reported.

System Organ Class	XINDEX Side Effects
Infections and infestations	
Less frequent:	Candidiasis (otitis externa fungal).
Immune system disorders	
Frequency unknown:	Hypersensitivity.
Psychiatric disorders	
Less frequent:	Irritability and crying.
Nervous system disorders	
Less frequent:	Paraesthesia (tingling in the ear), dizziness, headache.
Eye disorders	
Frequency unknown:	Blurred vision.
Ear and labyrinth disorders	
Frequent:	Ear discomfort and pain.
Less frequent:	Otorrhoea, ear congestion, ear pruritus, ear infection fungal, tinnitus, ear disorder, cerumen impaction, hypoacusis, medication residue present.
Frequency unknown:	Auricular swelling.
Vascular disorders	
Less frequent:	Flushing.
Gastrointestinal disorders *Less frequent:*	Vomiting, dysgeusia.
Skin and subcutaneous tissue disorders	
Less frequent:	Skin exfoliation, rash scaly, rash, rash erythematous.

Musculoskeletal and connective tissue disorders	
Frequency unknown:	Tendon inflammation.
General disorders and administration site conditions	
Less frequent:	Device occlusion (tympanostomy tube obstruction), fatigue, medication residue.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of XINDEX is important. It allows continued monitoring of the benefit/risk balance of XINDEX.

Healthcare professionals are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Gen-Eye (Pty) Ltd via email: pharmacovigilance@gen-eye.co.za or telephonically on 011 312 3812. Suspected adverse reactions can also be reported to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The limited holding capacity of the ear canal for topical otic products practically precludes any overdosing of ciprofloxacin/dexamethasone as in XINDEX. No cases of overdose have been reported. However, oral ingestion of ciprofloxacin/dexamethasone resulting in overdose or long-term ototopical therapy may produce suppression of the Hypothalamic-Pituitary-Adrenal (HPA) Axis. Although decreases in paediatric growth velocity and/or suppression of cortisol plasma concentrations may be more pronounced after substantial overdose or prolonged treatment (e.g. several months) with ciprofloxacin/dexamethasone, the effect is expected to be transient (days to weeks) and easily reversible with no long-term sequelae.

Treatment of acute overdosage is generally by supportive and systemic therapy, and may initially include emesis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.16.2 Aural preparations

Pharmacotherapeutic group: Otological anti-infectives

ATC code: S02A A

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 microorganisms: 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.

Mechanism of resistance

In vitro resistance to 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.

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

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.

5.2 Pharmacokinetic properties

Ciprofloxacin

Absorption

Following a single bilateral 4-drops per ear (8 drops per administration) dose of the combination ear drop formulation in 25 paediatric patients, peak ciprofloxacin concentrations (C_{max}) were achieved within one hour and ranged from less than 0.50 ng/ml to 3.45 ng/ml, the mean plasma ciprofloxacin Cmax 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 Cmax (1.33 ng/ml) was ~570-fold lower than the mean Cmax 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

Absorption

Following a single bilateral 4-drops per ear (8 drops per administration) dose of the combination ear drop formulation in 24 paediatric patients, peak dexamethasone concentrations (C_{max}) were achieved within one hour, the mean plasma dexamethasone Cmax 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 ~8.8-fold lower than the mean Cmax 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.

Systemic exposure

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 ciprofloxacin and dexamethasone 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity.

There is no evidence that the topical otic administration of ciprofloxacin/dexamethasone 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 ciprofloxacin/dexamethasone ear drops for one month exhibited no drug related structural or functional changes of the cochlear hair cells and no lesions in the ossicles.

Mutagenic and Carcinogenic potential:

Available data of genetic toxicology tests with ciprofloxacin and dexamethasone did not show evidence for a biologically relevant mutagenic potential for the topical otic application of ciprofloxacin/dexamethasone.

No long-term studies of ciprofloxacin/dexamethasone have been performed to evaluate carcinogenic potential.

Reproduction Toxicity

Topical dermal studies in animals have shown effects on male sex organs following long-term use of dexamethasone at doses much higher than those resulting from the use of ciprofloxacin/dexamethasone.

Reproduction studies performed in rats and mice at doses up to six-times the usual daily human oral dose revealed no evidence of impaired fertility or harm to the foetus due to 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate dihydrate
Sodium acetate trihydrate
Glaceal acetic acid

Mannitol
Tyloxapol
Glycerin
Hydroxypropylmethylcelullose
Sodium Hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 2 years
After first opening: 30 days

6.4 Special precautions for storage

Store below 30°C. Do not freeze.
Keep bottle in the outer carton in order to protect from light.
Do not use more than 30 days after opening.

6.5 Nature and contents of container

Opaque white sterile 5 ml dropper bottle with a white sterile capillary plug and white sterile cap, containing 5 ml suspension.
The dropper bottle is contained in an outer cardboard carton.

6.6 Special precautions for disposal

The product should not be used for more than 30 days after first opening the container.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]
Unit 7, Royal Palm Business Estate
646 Washington Street
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8. REGISTRATION NUMBER

49/16.2/0071

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 October 2022

10. DATE OF REVISION OF THE TEXT

Not applicable

[1] Company Registration Number.: 2009/009360/07

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