1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OTIXAL 3 mg/0,25 mg per 1 ml ear drops solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of OTIXAL contains 3 mg of ciprofloxacin (as hydrochloride monohydrate) and 0,25 mg of fluocinolone acetonide.

Preservatives:

Methyl parahydroxybenzoate 0,06 % *m/v*

Propyl parahydroxybenzoate 0,03 % *m/v*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops solution

OTIXAL is a colourless or slightly yellow, clear aqueous solution without visible particulate matter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

OTIXAL is indicated in patients aged 6 months and older for the treatment of infections caused by susceptible isolates of the designated microorganisms in:

- Acute otitis externa (AOE) due to *Staphylococcus aureus,* and *Pseudomonas aeruginosa,*

- Acute otitis media in patients with tympanostomy tubes (AOMT) due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Pseudomonas aeruginosa*.

4.2. Posology and method of administration

Posology

Adults and children aged 6 months and older

Instil 6 to 8 drops in the affected ear twice a day for 7 days.

Paediatric population

The safety and efficacy of OTIXAL in children younger than 6 months has not yet been established.

Method of administration

Auricular use.

Precautions to be taken before handling or administering OTIXAL

The solution should be warmed before its use, by holding the bottle in the hand for several minutes. This will avoid the discomfort that may result from the instillation of a cold solution into the ear canal. The patient should lie with the affected ear upward and then for patients with otitis externa the drops should be instilled pulling several times on the auricle. For patients with acute otitis media with tympanostomy tubes, the tragus should be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for around 1 minute to facilitate penetration of the drops into the ear.

Repeat, if necessary, for the opposite ear.

4.3. Contraindications

OTIXAL is contraindicated in:

- Patients with hypersensitivity to ciprofloxacin hydrochloride, fluocinolone acetonide or any member of the quinolone class of antimicrobial medicine, or to any excipients in OTIXAL (see section 6.1).
- Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

4.4. Special warnings and precautions for use

OTIXAL is for auricular use only, not for ophthalmic use, inhalation or injection.

OTIXAL should not be swallowed or injected.

Anaphylactic reactions

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.

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. If after the treatment some signs and symptoms persist, further evaluation is recommended to reassess the disease and the treatment.

Skin rash

OTIXAL should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Superinfection

As with other antibiotic preparations, the use of OTIXAL may result in overgrowth of non-susceptible organisms, including bacterial strains, yeast and fungi. If superinfection occurs, appropriate therapy should be initiated.

Photoallergic reactions

Some patients taking systemic quinolones have shown moderate to severe skin sensitivity to the sun. Due to the site of administration, it is unlikely that OTIXAL may produce photoallergic reactions.

Corticosteroids

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 OTIXAL.

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.

Paediatric population

Safety and efficacy of OTIXAL has not been established in children younger than 6 months.

4.5. Interaction with other medicines and other forms of interaction

No interaction studies have been performed with OTIXAL. However, due to negligible plasma levels observed after application in the ear (see section 5.2), it is unlikely that ciprofloxacin or fluocinolone acetonide, as contained in OTIXAL, may show clinically meaningful systemic interaction with other medicines.

Warfarin

The systemic administration of some quinolones, as contained in OTIXAL, has been shown to enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving ciclosporin concomitantly.

Caffeine, Theophylline

Oral administration of ciprofloxacin, as contained in OTIXAL, 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 OTIXAL, ciprofloxacin plasma concentrations are low, and it is unlikely that an interaction involving P450 metabolism with concomitant medicines would result in clinically relevant changes in plasma levels of methylxanthine compounds.

It is recommended not to use other ear preparations concomitantly. If more than one medicine needs to be administered by this route, it is advised to administer them apart.

4.6. Fertility, pregnancy and lactation

The safety of OTIXAL in pregnancy and lactation has not been established.

Pregnancy

As there is very little systemic absorption, OTIXAL may be used during pregnancy.

Breastfeeding

As there is very little systemic absorption, OTIXAL may be used during breastfeeding.

Fertility

No animal studies have been performed to evaluate the effect on fertility of OTIXAL.

4.7. Effects on ability to drive and use machines

OTIXAL has no or negligible influence on the ability to drive and operate machinery due to the route of administration and the conditions of use.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that OTIXAL do not adversely affect their ability to do so safely (see section 4.4 and 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Candidiasis, ear infection fungal, contralateral otitis media	
Nervous system disorders	Dysgeusia	Paraesthesia (tingling in ears), dizziness, headache, crying	
Eye disorders			Vision, blurred (see also section 4.4)
Ear and labyrinth disorders	Ear pain, ear discomfort, ear pruritus	Hypoacusis, tinnitus, otorrhoea, ear congestion, tympanic membrane disorder, auricular swelling	

Vascular disorders		Flushing	
Gastrointestinal disorders		Vomiting	
Skin and subcutaneous tissue disorders		Skin exfoliation, rash erythematous, rash, granulation tissue	
General disorders and administrative site conditions		Irritability, fatigue	
Investigations		Medicine residue	
Injury, poisoning and procedural complications		Device occlusion (tympanostomy tube obstruction)	

b) Description of selected adverse reactions

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. 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 and these musculoskeletal and connective tissue adverse reactions.

c) Paediatric population

OTIXAL has been shown to be safe in paediatric patients 6 months of age or older.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

No case of overdose has been reported.

Due to negligible plasma levels observed after application in the ear, it is unlikely that topically applied ciprofloxacin or fluocinolone acetonide may show clinically meaningful systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear.

The limited holding capacity of the ear canal for topical otic products practically precludes overdosing via the ototopical route. However, oral ingestion of OTIXAL 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 OTIXAL, the effect is expected to be transient (days to weeks) and easily reversible with no long-term sequelae.

Treatment

If OTIXAL is accidentally swallowed, treatment will include the administration of activated charcoal and antacids containing magnesium or calcium.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 16.2 Aural preparations.

Pharmacotherapeutic group: Otological preparations: corticosteroids and antiinfectives in combination

ATC code: S02CA05

Mechanism of action

Ciprofloxacin

As a fluoroquinolone antibacterial medicine, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

Mechanism of resistance

The mutation in genes encoding ciprofloxacin targets (gyr A, gyrN, parC, parE) represent the main mechanism of ciprofloxacin resistance in *P. aeruginosa*. Another mechanism of resistance described is overexpression of the efflux pumps, in particular Mex (Multiple EffluX) gene. The single mutations do not necessarily result in clinical resistance, but multiple mutations generally result in clinical resistance.

Fluocinolone acetonide

Fluocinolone acetonide is a synthetic fluorinated corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictive properties and reduces the formation of granulation tissue. Early anti-inflammatory effects of topical corticosteroids include the inhibition of macrophage and leukocyte movement and activity in the inflamed area by reversing vascular dilation and permeability. Later inflammatory processes such as capillary production, collagen deposition, keloid (scar) formation also are inhibited by corticosteroids.

5.2. Pharmacokinetic properties

Auricular use

Blood samples were taken in two studies of AOMT to determine the plasma levels of ciprofloxacin and/or fluocinolone acetonide. Pharmacokinetic analysis showed no or negligible plasma level of the active ingredients demonstrating that topical application of OTIXAL in the ear is unlikely to result in pharmacokinetically or clinically relevant systemic levels of ciprofloxacin and/or fluocinolone acetonide.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Compound of glycerine and ethylene oxide, diethylene glycol monoethylether, hydrochloric acid (as pH adjuster), methyl parahydroxybenzoate, povidone, propyl parahydroxybenzoate, purified water, sodium hydroxide (as pH adjuster).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

After first opening: 1 month

6.4. Special precautions for storage

Store at or below 30 °C.

After first opening: Store at or below 25 °C.

6.5. Nature and contents of container

1 x 10 ml white, low density polyethylene (LDPE) bottle fitted with a low density polyethylene dropper. The bottle is closed with a white, high density polyethylene (HDPE) screw cap, labelled, and packed into a cardboard carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

56/16.2/0942

9. DATE OF FIRST AUTHORISATION

23 July 2024

10. DATE OF REVISION OF TEXT

23 July 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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