PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrOTIXAL™

Ciprofloxacin and Fluocinolone acetonide Otic Solution
0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide

Antibacterial - Corticosteroid

Pediapharm Inc.
1 Place du Commerce, Suite 225,
Verdun, QC H3E 1A2

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OTIXAL™

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Otic	Otic Solution/ 0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) / 0.025% w/v fluocinolone acetonide	none *For a complete listing see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) otic solution is indicated for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric patients (age 6 months and older) due to *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis* and *Pseudomonas aeruginosa.*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of OTIXAL and other antibacterial drugs, OTIXAL should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

Geriatrics (> 65 years of age):

Clinical safety and efficacy of OTIXAL in sufficient patients aged 65 and over have not been established to determine whether they responded differently from children.

Pediatrics (< 6 months of age):

The safety and efficacy of OTIXAL in pediatric patients less than 6 months of age have not been studied. (See WARNINGS AND PRECAUTIONS, CLINICAL TRIALS)

CONTRAINDICATIONS

OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) is contraindicated in patients with known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any other ingredient of the formulation.

Use of this product is contraindicated in viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

WARNINGS AND PRECAUTIONS

General

OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) is for otic use only. It is not for ophthalmic use, or for oral/injection use.

Immune and Hypersensitivity

OTIXAL should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require immediate emergency treatment. 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.

Sensitization and irritation due to dermal applications of topical corticosteroids have been noted. Allergic contact dermatitis from topical corticosteroids is usually diagnosed by observing failure to heal rather than clinical exacerbation. If patient fails to recover following 7 days of treatment an appropriate therapy should be instituted.

Neurologic

Absorption of topical corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression and the potential for adrenal insufficiency after sudden withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glycosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. The risk of such effects is very low with OTIXAL as it is negligibly absorbed following otic administration.

Susceptibility/Resistance

Development of Drug-Resistant Bacteria:

Prescribing OTIXAL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of resistant organisms.

Potential for Microbial Growth:

As with other antibacterial products, use of this product may result in overgrowth of non-

susceptible bacteria, yeast and fungi. If such infections occur, discontinue use and institute alternative therapy.

If the infection is not improved following the full course of OTIXAL therapy (7 days 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 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The use of OTIXAL may promote the selection on non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Special Populations

Pregnant Women:
There are no adequate and well-controlled studies of OTIXAL in pregnant women. OTIXAL should not be used in pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Fluocinolone acetonide when administered subcutaneously induced abortions in rabbits. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Animal reproduction studies have not been conducted with OTIXAL. Ciprofloxacin is not teratogenic. (See TOXICOLOGY).

Nursing Women:
No adequate and well-controlled studies of OTIXAL have been conducted in nursing women. Ciprofloxacin or corticosteroids, as a class, appear in human milk after oral administration. It is not known whether otic administration of ciprofloxacin and fluocinolone acetonide could result in sufficient systemic absorption to produce detectable quantities in human milk. Due to the potential for unwanted effects from ciprofloxacin and fluocinolone acetonide in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother. (See TOXICOLOGY).

Pediatrics (< 6 months of age):
Myringotomy with tympanostomy tube placement is generally not performed in children less than 6 months of age. Safety and efficacy of OTIXAL in infants below 6 months of age has not been established. OTIXAL should not be administered in children less than 6 months of age.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In two clinical trials, 224 patients with acute otitis media with tympanostomy tubes were treated with OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) otic solution twice daily for a median duration of 7 days. Comparator groups were otic solutions of ciprofloxacin 0.3% w/v (n= 220) and fluocinolone acetonide 0.025% w/v (n=213). Subjects in these two trials were aged 6 months to 12 years, 385 (58.6%) of which were younger than 3 years of age.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the two trials, no treatment related serious adverse events were reported. The percentage of patients who discontinued the study medication due to adverse events was lower in the OTIXAL group (1.8%) than in the comparator groups (ciprofloxacin 0.3% w/v, and fluocinolone acetonide 0.025 % w/v). Adverse events leading to discontinuation were generally associated with otitis (otitis media and acute otitis media, and otitis externa) and conditions associated with otitis (such as rhinitis and streptococcal pharyngitis), and events such as ear pain and otorrhea.

The following treatment related adverse events occurred in at least 1 patient:

Table 1: Treatment Related Adverse Events that Occurred in at least 1 Patient

Adverse Event	OTIXAL (N=224) n (%)	CIPRO (N=220) n (%)	FLUO (N=213) n (%)
Ear and labyrinth disorders	4 (1.8%)	4 (1.8%)	5 (2.3%)
Auricular swelling	1 (0.4%)	0	1 (0.5%)
Ear pain	1 (0.4%)	1 (0.5%)	2 (0.9%)
Ear pruritus	1 (0.4%)	1 (0.5%)	0
Otorrhea	1 (0.4%)	1 (0.5%)	2 (0.9%)
Tympanic membrane disorder	1 (0.4%)	0	0
Deafness neurosensory	0	1 (0.5%)	0
Ear discomfort	0	1 (0.5%)	0
Ear haemorrhage	0	0	1 (0.5%)
Infections and infestations	1 (0.4%)	2 (0.9%)	2 (0.9%)
Contralateral otitis media	1 (0.4%)	0	0
Ear infection fungal	0	0	1 (0.5%)
Otitis externa	0	1 (0.5%)	0

Otitis externa Candida	0	1 (0.5%)	0
Sinusitis	0	0	1 (0.5%)
Skin and subcutaneous tissue disorders	2 (0.9%)	2 (0.9%)	4 (1.9%)
Excessive granulation tissue	1 (0.4%)	0	1 (0.5%)
Rash	1 (0.4%)	0	2 (0.9%)
Dermatitis	0	1 (0.5%)	0
Eczema	0	1 (0.5%)	1 (0.5%)

A total of 22.4% (148 / 662) of the children from the two trials reported bilateral ear infection at baseline. The percentage of adverse events in children treated with OTIXAL was similar in children with unilateral ear infection (4.4%) and bilateral infection (4.7%).

The overall incidence of adverse events was greater in the subgroup of children younger than 3 years. For these children, the incidence of adverse events was similar between treatment groups. The number of children with at least one adverse event was slightly lower in the OTIXAL group (70 of 132 patients, 53.0%) in children younger than 3 years as compared with (26 of 92 patients, 28.3%) children 3 years and older.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified with use of ciprofloxacin 0.3% w/v and fluocinolone acetonide 0.025% w/v otic solution in ear infections. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ear and labyrinth disorders: auricular swelling, ear pain, tinnitus, ear congestion, vertigo
- General disorders and administration site conditions: administration site pain, application site stinging, localized oedema, pain, pruritus, pyrexia
- Immune system disorders: allergic reaction
- Infections and infestations: candidiasis
- Injury, poisoning and procedural complications: device occlusion (tympanostomy tube obstruction)
- Nervous system disorders: paresthesia (tingling in ears), dysgeusia, dizziness, headache
- Skin and subcutaneous tissue disorders: skin exfoliation, rash erythematous

From other otic drug products containing ciprofloxacin 0.3% w/v or 0.01 - 0.025% w/v fluocinolone acetonide following adverse reactions are noted:

- Cardiac disorders: tachycardia
- Ear and labyrinth disorders: decreased hearing, deafness neurosensory, myringitis, external eczematous otitis
- Immune system disorders: hypersensitivity, allergic dermatitis, allergic skin reactions, face red, rash, urticarial, laryngeal edema severe, angioedema
- Eye disorders: visual acuity reduced

- Investigations: thrombopenia
- Nervous system disorders: vestibular vertigo
- Metabolism and nutrition disorders: non insulin dependent diabetes mellitus

DRUG INTERACTIONS

No interaction studies (i.e., drug-drug, drug-food, drug-herb, drug-laboratory tests) have been conducted with OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide). Given the low systemic concentrations of ciprofloxacin and fluocinolone acetonide following topical otic administration of OTIXAL to the human ear, drug-drug interactions at the systemic level are unlikely to occur.

Drug-Lifestyle Interactions

OTIXAL has no influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) is for otic use only. It is not for ophthalmic use, or for oral/injection use.

OTIXAL should not be used in children less than 6 months of age.

Recommended Dose and Dosage Adjustment

The contents of one single use vial (deliverable volume: 0.25 mL) of OTIXAL should be instilled into the affected ear canal twice daily (approximately every 12 hours) for 7 days. This dosing regimen should be used for children of 6 months of age and older.

The solution should be warmed by holding the vial in the hand for 1 or 2 minutes. This is to avoid dizziness, which may result from the instillation of a cold solution into the ear canal.

The patient should lie with the affected ear upward, and then the medication should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear. This position should be maintained for 1 minute. Repeat, if necessary, for the opposite ear.

Missed Dose

If a dose of OTIXAL is missed, it should be given as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule should be followed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Overdose with OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) is unlikely due to the unit dose package.

If the preparation is accidentally swallowed, treatment will include gastric emptying by induced vomiting or gastric lavage, the administration of activated charcoal and antacids containing magnesium or calcium. Further management should be as clinically indicated or as recommended by the regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

OTIXAL contains ciprofloxacin, an antibacterial drug, and fluocinolone acetonide, a corticosteroid.

Ciprofloxacin, a fluoroquinolone, is a broad spectrum antibiotic, has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA (see MICROBIOLOGY).

Fluocinolone acetonide has anti-inflammatory, antipruritic, and vasoconstrictive properties. It inhibits the local biosynthesis of prostaglandins, which explains part of its anti-inflammatory efficacy. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A_2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system.

Pharmacodynamics

The pharmacology of ciprofloxacin 0.3% w/v and 0.025% w/v fluocinolone acetonide has not been studied. Individually, ciprofloxacin and fluocinolone acetonide have been well characterized in the literature.

Pharmacokinetics

In two pivotal phase 3 studies of acute otitis media with tympanostomy tubes in children aged 6 months to 12 years, blood samples were taken in subgroups of 14 and 11 patients, at Visit 1 (prior to the first dose) and Visit 3 (within 1 and 2 hours after the last dose) respectively, to determine the plasma levels of ciprofloxacin and/or fluocinolone acetonide. Three children treated with OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v

fluocinolone acetonide) or ciprofloxacin 0.3% w/v alone had bilateral ear infection. Only one child with bilateral ear infection demonstrated a detectable level of ciprofloxacin (3.0 ng/mL) in plasma after 7 days of treatment. Detectable concentrations (lower limit of quantification = 1 ng/mL) of ciprofloxacin or fluocinolone acetonide in plasma were not observed in children with unilateral ear infection after 7 days of treatment.

Maximum daily exposures consisted of the otic application of approximately 1.5 mg of ciprofloxacin and 0.125 mg of fluocinolone acetonide per day over the treatment period, with double this amount for bilateral inner ear infection. Considering the ciprofloxacin systemic exposure, the concentrations achieved with the otic administration were approximately 450-fold lower than those obtained in human serum following an oral dose of 250 mg.

Special Populations and Conditions

No specific studies in special patient populations have been performed with OTIXAL. No differences in the pharmacokinetics of OTIXAL are expected in these populations due to the topical administration of the product.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C). Protect from light; store unused vials in pouch and discard 7 days after opening the pouch. Do not open until ready to use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) is a sterile, preservative-free otic solution containing ciprofloxacin 0.3% w/v (3 mg/mL) and fluocinolone acetonide 0.025% w/v (0.25 mg/mL).
Non-medicinal ingredients: polysorbate 80, glycerin, povidone K90F and purified water.

OTIXAL is packaged in a low-density translucent polyethylene single-use vial (0.25 mL each) contained in an aluminium foil overwrap pouch and a carton box for protection against light. OTIXAL is available in the following formats:

- Fifteen vials, divided in three strips of five vials, are packed per pouch.
- Forty-eight vials divided into twenty-four pouches, strips of two vials per pouch.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

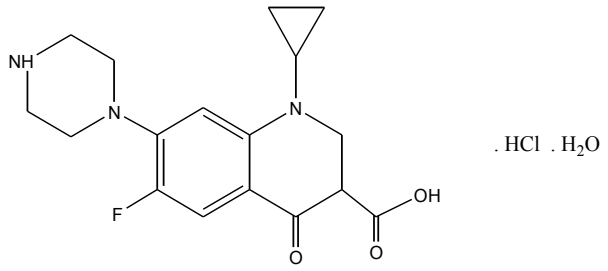
Proper name: Ciprofloxacin hydrochloride

Chemical name:

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate

Molecular formula and molecular mass: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$, 385.8

Structural formula:



. HCl . H_2O

Physicochemical properties:

Description:	Pale yellow crystalline powder.
Physical Form:	Ciprofloxacin hydrochloride does not exist in different polymorphic forms.
Solubility:	Sparingly soluble in water; slightly soluble in acetic acid, methanol; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, acetonitrile, ethyl acetate, hexane and methylene chloride.
Hygroscopicity:	Ciprofloxacin hydrochloride is not hygroscopic.
Melting point:	318 - 320°C.

Drug Substance

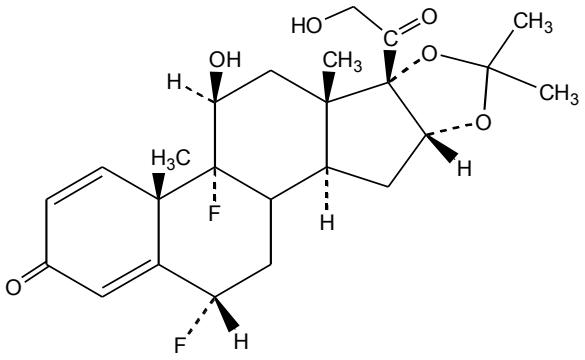
Proper name: Fluocinolone Acetonide

Chemical name:

6α, 9 α -difluoro-11β,16α,17,21-tetrahydroxypregna- 1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone

Molecular formula and molecular mass: $C_{24}H_{30}F_2O_6$, 452.49

Structural formula:



Physicochemical properties:

Physical Description: White to almost white, crystalline powder.

Physical Form: The X-ray diffraction analyses demonstrated 3 polymorphic diffraction patterns.

Solubility: Soluble in methanol; slightly soluble in ether and chloroform and insoluble in water.

Hygroscopicity: Fluocinolone acetonide is not hygroscopic.

Melting point: Melts at about 270ºC, with decomposition.

CLINICAL TRIALS

Acute Otitis Media with Tympanostomy Tubes

Study Demographics and Trial Design

Two phase 3 multicenter, randomized, double-blind, active-controlled, parallel group trials were conducted in 662 pediatric patients (aged 6 months to 12 years) with uncomplicated acute otitis media with tympanostomy tubes (AOMT), to assess the efficacy and safety of OTIXAL (0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide) compared to ciprofloxacin 0.3% w/v otic solution (CIPRO) and to fluocinolone acetonide 0.025% w/v otic solution (FLUO). Minimum inclusion criteria were open tympanostomy tubes, otorrhea for 3 weeks or less, and moderate to severe purulent otorrhea. Unit dose (0.25 mL) solutions were administered to the affected ear(s) twice daily for 7 days. Investigators used both diary card information and otoscopic examination to ascertain the time to cessation of otorrhea at End of Treatment on Visit 3 (Day 8-10) and Test of Cure on Visit 4 (Day 18-22).

Table 2: Summary of Patient Demographics (ITT population) in Clinical Trials of OTIXAL in Patients with Acute Otitis Media with Tympanostomy Tubes

Trial #	Dosage*, route of administration and duration	Study subjects	Mean age (Range) years	Gender
Trial 1	OTIXAL CIPRO FLUO Otic solution (0.25 mL), administration by otic route, twice daily dose 7 days of treatment	112 109 110	3.2 (0.6-11.8) 3.5 (0.6-11.6) 3.5 (0.8-12.7)	M: 64; F: 48 M: 66; F: 43 M: 68; F: 42
Trial 2	OTIXAL CIPRO FLUO Otic solution (0.25 mL), administration by otic route, twice daily dose 7 days of treatment	111 112 108	3.2 (0.6-12.7) 3.3 (0.7-12.0) 3.2 (0.6-12.2)	M: 65; F: 46 M: 69; F: 43 M: 59; F: 49

*Total Dosage for unilateral AOMT infection: 1.5 mg ciprofloxacin and 0.125 mg of fluocinolone acetonide administered twice daily by otic route. Total dose was approximately 10.5 mg of ciprofloxacin and 0.875 mg of fluocinolone acetonide over a 7-day period.

ITT = Intent-to-treat; CIPRO= Ciprofloxacin 0.3% w/v otic solution; FLUO=Fluocinolone acetonide 0.025% w/v otic solution; M=Male; F=Female

The primary endpoint in both trials was to demonstrate therapeutic superiority of OTIXAL relative to ciprofloxacin alone and to fluocinolone acetonide alone for time to cessation of

otorrhea. Otorrhea was defined as ending on the first day on which the otorrhea was absent and remained absent until the end of the trial. The primary analysis was performed on the clinical intent-to-treat (CITT) population.

Trial Results

In both AOMT trials OTIXAL resulted in statistically significantly shorter time to cessation of otorrhea than ciprofloxacin alone and fluocinolone acetonide alone in the CITT population. Time to cessation of otorrhea was not estimable for the fluocinolone acetonide group because the number of censored patients was greater than the number of patients with cessation of otorrhea. Sensitivity analysis for time to cessation of otorrhea provided similar results in the clinical per-protocol population (CPP).

Table 3: Time (Days) to Cessation of Otorrhea (CITT Population)

	Treatment arm		
Trial 1	**OTIXAL (N=112)**	**CIPRO (N=109)**	**FLUO (N=110)**
Number (%) of patients with cessation of otorrhea by Day 22	88 (78.6%)	73 (67.0%)	53 (48.2%)
Median time to cessation of otorrhea including censored* patients** (Min/Max)	3.8 (3.0 / 4.4)	7.7 (4.8 / 11.4)	n.e. (7.4 / n.e.)
Log-rank test p-value vs OTIXAL***		<0.001	<0.001
Trial 2	**OTIXAL (N=111)**	**CIPRO (N=112)**	**FLUO (N=108)**
Number (%) of patients with cessation of otorrhea by Day 22	87 (78.4%)	77 (68.8%)	47 (43.5%)
Median time to cessation of otorrhea including censored* patients** (Min/Max)	4.9 (3.7 / 5.5)	6.8 (5.5 / 7.7)	n.e. (13.9 / n.e.)
Log-rank test p-value vs OTIXAL***		0.028	<0.001

n.e.: not estimable because the number of censored patients was greater than the number of patients with cessation of otorrhea

*Censored: Subjects with otorrhea still present at end of the study, and those who discontinued for any reason or took rescue medication were censored at Day 22.

** Kaplan-Meier median estimate censored all subjects who did not have a cessation of otorrhea at the maximum time point of 22 days.

*** Log-rank test stratified by age (patients younger than 3 years versus 3 years and older)

CITT=Clinical intent-to-treat; CIPRO=Ciprofloxacin 0.3% w/v otic solution; FLUO=Fluocinolone acetonide 0.025% w/v otic solution; SD=standard deviation.

Middle ear fluid aspiration via the tympanostomy tube at Visit 1 did not yield a cultureable pathogen in 29.3% children. Higher bacterial eradication was reported with OTIXAL as compared with comparator arm (Table 4).

Table 4: Per Pathogen Based Bacterial Eradication Rates - Microbiological Evaluable* Patient Population from Acute Otitis Media with Tympanostomy Tubes Studies

	OTIXAL n/N (%)		**CIPRO (0.3% w/v) n/N (%)**	
	Visit 3	**Visit 4**	**Visit 3**	**Visit 4**
P. aeruginosa	16/17 (94.1%)	16/16 (100%)	12/14 (85.7%)	12/13 (92.3%)
S. aureus	25/28 (89.3%)	24/25 (96%)	26/33 (78.8%)	21/22 (95.5%)
M. catarrhalis	13/13 (100%)	13/13 (100%)	10/10 (100%)	11/11 (100%)
H. influenzae	20/21 (95.2%)	17/18 (94.4%)	31/31 (100%)	26/27 (96.3%)
S. pneumoniae	10/10 (100%)	7/7 (100%)	10/10 (100%)	11/11 (100%)

*Microbiological Evaluable = microbiological per-protocol population (all per-protocol patients whose Visit 1 was positive and who had microbiological results from Visit 3 and/or Visit 4)
n=number of patients with microbiological eradication or presumed eradication
N=total number of patients with microbiological response

In children with unilateral ear infection, median time to cessation of otorrhea were 4.1 days for OTIXAL (n=180), 7 days for ciprofloxacin 0.3% w/v (n=165), and not estimable for fluocinolone acetonide 0.025% w/v (n=169). The log-rank test and Wilcoxon test among unilateral ear infection subjects were statistically significant in the time to cessation of otorrhea between the OTIXAL and the ciprofloxacin groups and between the OTIXAL and the fluocinolone acetonide groups ($p<0.001$ for all comparisons). However in children with bilateral ear infection median time to cessation of otorrhea were 6.6 days in the OTIXAL group (n=43), 6.9 days in the ciprofloxacin group (n=56) and not estimable in the fluocinolone acetonide group (n=49). The log-rank test and Wilcoxon test among bilateral subjects were not statistically significant in the time to cessation of otorrhea between the OTIXAL and the ciprofloxacin groups, but were statistically significant between the OTIXAL and the fluocinolone acetonide groups ($p=0.022$ and $p=0.019$, respectively).

One third of the children with severe otorrhea at baseline reported a shorter time to cessation with OTIXAL administration compared with children who received the individual ingredients (median (days): 4.3 OTIXAL; 15.5 ciprofloxacin; not estimable for fluocinolone acetonide).

In the CITT population, time to cessation of otorrhea was shorter (median 3.7 days) in children 3 years and older than children younger than 3 years (median 4.9 days) with OTIXAL.

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA (see MICROBIOLOGY).

Like other topical corticosteroids, fluocinolone acetonide has anti-inflammatory, antipruritic, and vasoconstrictive properties. It aids in the resolution of the inflammatory response accompanying bacterial infection.

MICROBIOLOGY

The bactericidal action of ciprofloxacin results from the inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV enzymes, which are required for bacterial DNA replication, transcription, repair, and recombination.

Bacterial resistance to quinolones can develop through chromosomal or plasmid-mediated mechanisms.

In vitro studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

In vitro activity of ciprofloxacin against bacterial isolates associated with otitis externa and otitis media is reported in Table 5.

Table 5: Ciprofloxacin *in vitro* Data against Organisms associated with AOE and AOMT

Pathogen	N	MIC range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
P. aeruginosa	71	≤ 0.12 - 1	≤ 0.12	0.5
S. aureus	51	≤ 0.12 - 512	0.5	16
M. catarrhalis	100	≤ 0.12	≤ 0.12	≤ 0.12
H. influenzae	100	≤ 0.12 - 8	≤ 0.12	≤ 0.12
S. pneumoniae	102	0.5 - 8	1	2

MIC=Minimum inhibitory concentration; AOE=Acute otitis externa; AOMT=Acute otitis media with tympanostomy tubes
Isolate collection: 2012- 2014

Methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered a resistant organism to ciprofloxacin.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies of ciprofloxacin and fluocinolone acetonide have been conducted in several species, and the corresponding LD_{50} have been determined. In rabbits, when ciprofloxacin was instilled as a single dose in the middle ear cavities a reversible mild inflammatory response was seen in the tympanic membrane.

Table 6: LD_{50} Values for Ciprofloxacin

Animal	Method of Administration	LD_{50} (mg/kg)
Mouse	Intravenous	122
	Oral	5000
	Subcutaneous	> 1000
	Intraperitoneal	1165
Rat	Intravenous	207
	Oral	> 2000
	Subcutaneous	> 1000
Rabbit	Oral	2500
Cat	Oral	150
Dog	Oral	NA

LD_{50}=Median lethal dose; NA= not available

Table 7: LD_{50} Values for Fluocinolone Acetonide

Animal	Route	LD_{50} (mg/kg)
Mouse	Oral	> 4000
	Subcutaneous	200
	Intraperitoneal	103
Rat	Oral	>4000
	Subcutaneous	108
	Intraperitoneal	42
Guinea-pig	Subcutaneous	> 3170

LD_{50}=Median lethal dose

Repeat-Dose Toxicity

Guinea pigs were used to assess the otic tolerance and toxicity after repeated topical otic administration for 4 weeks of ciprofloxacin 0.3% w/v and fluocinolone acetonide 0.025% w/v. The guinea pigs (3 males/3 females) were administered 20 µL of the drug product daily in the right outer ear canal for 28 days (0.06 mg/day ciprofloxacin and 0.005 mg/day fluocinolone acetonide; 1.68 mg ciprofloxacin and 0.14 mg fluocinolone acetonide over the course of the study). The left ear was used as control. There were no mortalities and no significant differences in body weight measurements. No signs of skin irritation were noted; however, fluocinolone acetonide may have decreased the appearance of skin inflammation. In the histological examination of the control and treated ears sections, one male animal had a mild vascular congestion of the submucosa along with mild focal mononuclear infiltrates. No other histological differences were noted between the treatment and control groups.

A subacute ototoxicity study in guinea pigs was performed to evaluate the potential ototoxicity of OTIXAL plus degradation products when administered via the intratympanic route. Test and control were administered by 50 µL bolus infusion through a surgically implanted catheter into the middle ear twice daily (corresponding to 0.3 mg/day of ciprofloxacin and 0.025 mg/day of fluocinolone acetonide) for 28 days, and Auditory Brainstem Response (ABR) evaluations were performed on all animals at 2 designated times (Pre-test and Day 29). OTIXAL and the vehicle control did not produce mortality, and were without effect on clinical observations, body weights, physical examinations, otoscopic examinations, macroscopic evaluations, ossicle mobility, cytocochleograms, or middle ear assessments. In the OTIXAL group, mild mean ABR threshold elevations were observed on Day 29 compared to pretest at 10 and 20 kHz, but not at 4 kHz.When considering the male and female animals separately, a mild and moderate mean ABR threshold elevation was observed in the female group at 10 and 20 kHz, respectively. Although this suggests a sensorineural hearing loss caused by the treatment, in the context of the overall assessment where no other ototoxicity changes were observed, the relevance of this isolated finding is low. The Neomycin positive control group showed severe hearing loss in both male and female animals, at each test frequency, with the largest ABR threshold elevation at 20 kHz. Neomycin produced expected toxicity in the middle ear, as detailed in the macroscopic observations, ossicles mobility, cytocochleograms, auditory brainstem responses, and middle ear assessments.

Carcinogenicity

The long-term carcinogenicity studies of ciprofloxacin in rats and mice resulted in no carcinogenic or tumorigenic effects when administered at oral doses up to 250 mg/kg/day (rats) and 750 mg/kg/day (mice) for up to two years. Furthermore, long-term, photo co-carcinogenicity tests have shown that ciprofloxacin does not reduce the time to appearance of ultraviolet light induced skin tumors in hairless mice.

The majority of studies dealing with fluocinolone acetonide's carcinogenic potential show that it is an inhibitor of chemically-induced tumors as well as an inhibitor of tumor promoter-induced formation of adducts when co-administered. Two studies in mice found some tumor enhancement effect of fluocinolone.

Long term animal studies have not been performed to evaluate the carcinogenic potential of OTIXAL.

Mutagenicity

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V79 Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Although 2 of the 8 tests were positive, results of the following 3 *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Fluocinolone acetonide was not found to be genotoxic *in vitro,* in the Ames test and the Mouse lymphoma TK assay, and *in vivo*, in the mouse bone marrow micronucleus assay.

Reproductive Toxicology

Animal reproductive studies have not been conducted with OTIXAL.

Reproduction studies performed in rats and mice using oral doses of up to 100 mg/kg and intravenous doses up to 30 mg/kg of ciprofloxacin revealed no evidence of harm to the fetus. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. 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. In monkeys, ciprofloxacin (0 - 200 mg/kg, oral and 0 - 25 mg/kg, parenteral – day 20-50 of pregnancy) was well tolerated and did not induce development changes of the embryo or fetus, increases in abortion or differences in hormone levels.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 1000 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of

ciprofloxacin from the ear of a patient treated with ciprofloxacin and fluocinolone acetonide twice daily according to label directions.

Ciprofloxacin at oral doses of 20 and 40 mg/kg administered to pregnant female rats (once daily for 20 days) induced general changes in the reproductive performance of female rats and significant alterations in the development of the skeletal parameters of fetuses.

No adequate animal reproduction studies have been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Fluocinolone acetonide, when administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 µg/kg/day caused abortions and malformations in a few surviving fetuses. When administered subcutaneously at a dose of 0.13 mg/kg/day, during days 6 to 18 of pregnancy in the rabbit, fluocinolone acetonide induced abortion at the end of the third and at the beginning of the fourth gestational week. The effect of subcutaneous administration of fluocinolone acetonide (single doses of 0.02, 0.1 and 0.5 mg/kg) on mortality and body weight gain in newborn rats (10-24 h following delivery) was analyzed. Administration at the highest dose (0.5 mg/kg) resulted in non survival. At lower dose levels, fluocinolone acetonide induced mortality and prevented normal body weight gain.

Local Tolerance Studies

Local tolerance of ciprofloxacin 0.3% w/v otic solution and ciprofloxacin 0.3% w/v and fluocinolone acetonide 0.025% w/v otic solution was assessed in two skin irritation studies in rabbits. In one study local tolerance of intact and abraded skin after administration of 0.3% w/v ciprofloxacin otic solution was assessed. Ciprofloxacin otic solution was well tolerated on intact skin. There was 1 mild case of erythema after application to abraded skin. The overall conclusion of the study was that ciprofloxacin 0.3% w/v otic solution was non-irritant. In addition, a study of primary dermal irritation in the rabbit assessed the degree of skin irritation caused by ciprofloxacin 0.3% w/v and fluocinolone acetonide 0.025% w/v otic solution when applied with a semi-occlusive patch to shaved rabbit skin for 4 hours. In the active substance group, two of the three animals presented with slight erythema which was accompanied by slight oedema in only one animal. In the vehicle substance group, two of the three animals presented with changes; one with well-defined erythema and slight oedema and another with slight erythema. No dermal lesions were observed seventy two hours after the removal of the patch in any animal. The study concluded that ciprofloxacin 0.3% w/v and fluocinolone acetonide 0.025% w/v otic solution is a non-irritant.

Local tolerance of OTIXAL was also evaluated in the local lymph node assay, a murine model to assess the skin sensitization potential of a product in the CBA/Ca strain mouse following topical application to the dorsal surface of the ear. The drug product was classified as a non-irritant and a non-sensitizer under the experimental conditions assayed. Furthermore, a study to assess the dermal irritant and/or corrosive effect was performed with OTIXAL in female New Zealand white rabbits. Neither injured skin nor mortality was observed and none of the animals showed weight loss during the study period. No anomaly was observed during macroscopical evaluation

of organs and tissues upon gross necropsy. Taking all the data together, OTIXAL is classified as a non-irritant and non-corrosive under the experimental conditions assayed.

Articular Tolerability Studies

The systemic administration of ciprofloxacin and other quinolones at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Topical ocular administration of ciprofloxacin to immature dogs did not cause any arthropathy. There is no evidence that the otic dosage form has any effect on the weight-bearing joints.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr OTIXAL™
(o'ti'ksal)
Ciprofloxacin and Fluocinolone acetonide Otic Solution
(0.3% w/v ciprofloxacin (as ciprofloxacin hydrochloride) and 0.025% w/v fluocinolone acetonide)

Read this carefully before you start taking **OTIXAL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OTIXAL**.

OTIXAL otic solution are ear drops intended for use in the ears only.
Do not use this medication in the eyes or take it by mouth.

What is OTIXAL used for?
OTIXAL is used to treat infection caused by certain bacteria in the middle ear of children 6 months and older who have a tube in the ear drum.

Antibacterial drugs like OTIXAL treat only bacterial infections. They do not treat viral infections. OTIXAL contains an antibacterial ingredient called ciprofloxacin, and it should be used exactly as directed and until the 7 days of treatment is completed. Misuse or overuse of OTIXAL could lead to the growth of bacteria that will not be killed by ciprofloxacin. This means that OTIXAL or other medicines that contain ciprofloxacin may not work for you in the future. Do not share your medicine.

How does OTIXAL work?
OTIXAL ear drops contain ciprofloxacin hydrochloride and fluocinolone acetonide. Ciprofloxacin hydrochloride kills bacteria. This treats the infection. Fluocinolone acetonide reduces the substances which inflame tissues. Together they treat the ear infection and swelling.

What are the ingredients in OTIXAL?
Medicinal ingredients: Ciprofloxacin hydrochloride and fluocinolone acetonide.
Non-medicinal ingredients: polysorbate 80, glycerin, povidone K90F and purified water.

OTIXAL comes in the following dosage forms:
OTIXAL is a sterile, preservative-free ear drop solution supplied in translucent single-use 0.25 mL vials. Vials are packaged in a protective foil pouch.

Do not use OTIXAL if:

- You/your child are allergic (hypersensitive) to ciprofloxacin or to other quinolone antibiotics.

- You/your child are allergic to fluocinolone acetonide or to other steroids.
- Children are younger than 6 months old.
- You/your child have an ear infection caused by a virus or fungus.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OTIXAL. Talk about any health conditions or problems you may have, including if:

- You have/your child has 2 or more ear infections within 6 months.
- You are breast-feeding a baby. It is not known if the active ingredients in these ear drops pass into breast milk.

Other warnings you should know about:

Contact your doctor:

- If you/your child develop:
  - A swelling
  - A serious skin rash
  - A pain or discharge lasting for a few days
- Before stopping OTIXAL treatment. Do not stop treatment on your own. These conditions may be caused by bacteria, yeast, or fungus resistant to the drug.

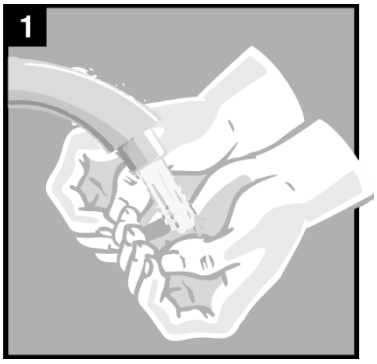
Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take OTIXAL:

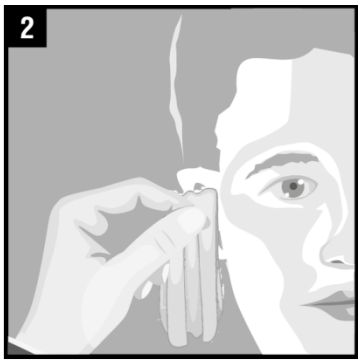
See the step-by-step instructions for using OTIXAL below.

It is important that the person giving OTIXAL follows these instructions carefully to make sure that the drug is most effective.

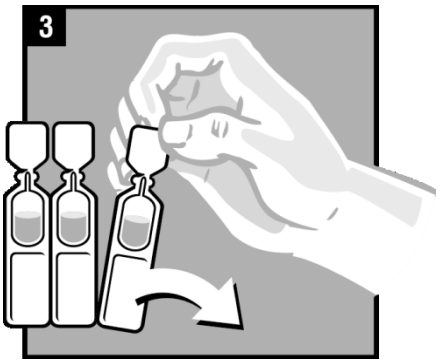
1. The person giving OTIXAL should wash his or her hands with soap and water.



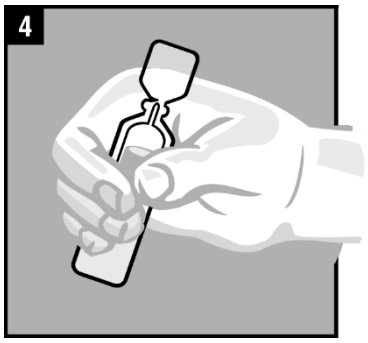
2. Gently clean any discharge that can be removed easily from the outer ear. DO NOT INSERT ANY OBJECT OR SWAB INTO THE EAR CANAL.



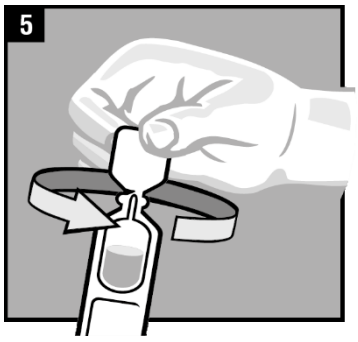
3. Detach the vial from the pack.



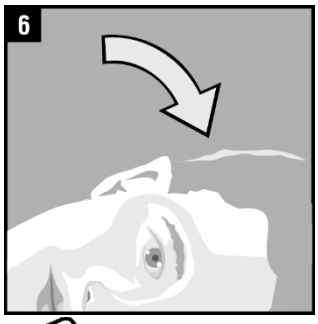
4. Warm the ear drops by holding the vial in your hands for 1 or 2 minutes.



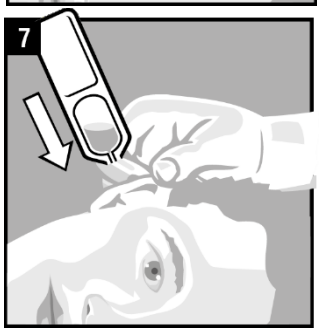
5. Twist off the vial cap.



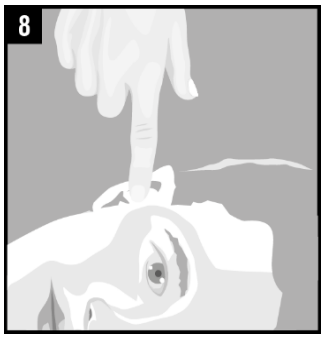
6. Tilt your/your child's head to one side to keep the affected ear up.



7. Instill the contents of 1 vial in the ear.

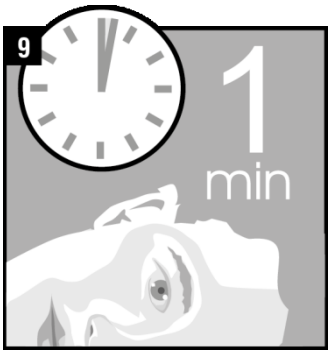


8. Pump the tragus (the small piece of cartilage found in front of the ear canal) 4 times by pushing inward to allow the medicine to penetrate the middle ear. This will allow the drops to pass through the tube in the eardrum and into the middle ear.



9. Keep the patient's head tilted sideways for approximately 1 minute to allow the medicine time to penetrate the ear. When instilling ear drops, raising the head to the vertical position or moving too rapidly may cause part of the medicine to leak out of the ear canal. This should be avoided as it may prevent the medicine from reaching the full depth of the ear canal.

   Discard the vial after the administration.



10. Repeat steps, if necessary, for the opposite ear.

Usual dose:

- Instill the contents of 1 single-use vial into the affected ear twice daily for 7 days. Use approximately every 12 hours, for example at 8 AM and 8 PM.
- Use this dosing routine for patients of all ages.

- Do not use OTIXAL unless your/your child's doctor has told you how to use it and you understand the explanation. Ask your/your child's doctor or pharmacist if you have any questions.
- Use OTIXAL exactly as your/your child's doctor has told you.
- Use the ear drops for as long as the doctor has instructed, even if the symptoms improve.
- Do not start or stop using OTIXAL without talking to your/your child's doctor first.

Overdose:

If OTIXAL is accidentally swallowed or if you think you have instilled too much into your ear, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you/your child miss a dose of OTIXAL, it should be given as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not use a double dose unless your/your child's doctor has instructed you to do so. If the infection is not improved after 1 week, you should consult your/your child's doctor.

What are possible side effects from using OTIXAL?

Common side effects with OTIXAL include:

- Itching, pain, discharge or swelling in the ear.

Tell your/your child's doctor if you have any side effects that bother you or do not go away.

These are not all the possible side effects you may feel when taking OTIXAL. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Allergic reactions: symptoms include: • swelling in the eyes, lips, mouth, tongue, face and throat • itching • rash • hives		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep out of reach and sight of children, preferably in a locked cupboard.

- Do not use after the expiry date that is stated on the carton and the vial.
- Store at room temperature (15°C to 30°C). Protect from light; store unused vials in the protective foil pouch and discard 7 days after opening the pouch. Do not open until ready to use.
- After using the full contents of the vial, discard the empty vial in a secure location.

If you want more information about OTIXAL:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.otixal.ca, or by calling 1-877-630-5674.

OTIXAL is a trademark from Laboratorios SALVAT, S.A., Spain and is distributed in Canada by Pediapharm under licence from Laboratorios SALVAT, S.A., Spain.

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