HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OTOVEL safely and effectively. See full prescribing information for OTOVEL.

OTOVEL (ciprofloxacin and fluocinolone acetonide) otic solution
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
OTOVEL is a combination of ciprofloxacin, a fluoroquinolone antibacterial, and fluocinolone acetonide, a corticosteroid, indicated for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric patients (aged 6 months and older) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa (1)*

----------DOSAGE AND ADMINISTRATION----------
- OTOVEL is for otic administration only. It is not for ophthalmic use, or for injection. (2)
- Instill the contents of one single-dose vial (0.25 mL) into the affected ear canal twice daily for 7 days. (2)
- Use this dosing regimen for patients aged 6 months and older. (2)

---------DOSAGE FORMS AND STRENGTHS----------
Otic Solution: Each single-dose vial of OTOVEL (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 %) delivers 0.25 mL of solution equivalent to ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg.

----------CONTRAINDICATIONS----------
OTOVEL is contraindicated in:
- Patients with known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any component of OTOVEL. (4)
- Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypersensitivity*: Discontinue use at the first appearance of a skin rash or any other sign of hypersensitivity. (5.1)
- *Potential for Microbial Overgrowth:* Prolonged use may result in the overgrowth of non-susceptible bacteria and fungi. If such infections occur, discontinue use and institute alternative therapy. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions that occurred in ≥1 patient were otorrhea, excessive granulation tissue, ear infection, ear pruritus, tympanic membrane disorder, auricular swelling and balance disorder (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arbor Pharmaceuticals at 1-866-516-4950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OTOVEL is indicated for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric patients (aged 6 months and older) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

2 DOSAGE AND ADMINISTRATION

- OTOVEL is for otic use only. It is not for ophthalmic use, or for injection.

The recommended dosage regimen is as follows:

- Instill the contents of one single-dose vial 0.25 mL into the affected ear canal twice daily (approximately every 12 hours) for 7 days. Use this dosing for patients aged 6 months of age and older.
- Warm the solution by holding the vial in the hand for 1 to 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 instill the medication.
- Pump the tragus 4 times by pushing inward to facilitate penetration of the medication into the middle ear.
- Maintain this position for 1 minute. Repeat, if necessary, for the opposite ear *[see Instructions for Use]*.

3 DOSAGE FORMS AND STRENGTHS

Otic Solution: Each single-dose vial of OTOVEL (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 %) delivers 0.25 mL of solution equivalent to ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg.

4 CONTRAINDICATIONS

OTOVEL is contraindicated in:

- Patients with known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any other components of OTOVEL.

- Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

OTOVEL should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema

(including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria and itching. Serious acute hypersensitivity reactions may require immediate emergency treatment.

5.2 Potential for Microbial Overgrowth with Prolonged Use

Prolonged use of OTOVEL may result in overgrowth of non-susceptible bacteria and fungi. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment. If such infections occur, discontinue use and institute alternative therapy.

5.3 Continued or Recurrent Otorrhea

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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 224 patients with AOMT were treated with OTOVEL for a median duration of 7 days. All the patients received at least one dose of OTOVEL. There were 220 patients who received at least one dose of ciprofloxacin (CIPRO) and 213 patients received at least one dose of fluocinolone acetonide (FLUO).

The most common adverse reactions that occurred in 1 or more patients are as follows:

Table 1: Selected Adverse Reactions that Occurred in 1 or more Patients in the OTOVEL Group

Adverse Reactions[1]	**Number (%) of Patients**		
	OTOVEL N=224	**CIPRO N=220**	**FLUO N=213**
Otorrhea	12 (5.4%)	9 (4.1%)	12 (5.6%)
Excessive granulation tissue	3 (1.3%)	0 (0.0%)	2 (0.9%)
Ear infection	2 (0.9%)	3 (1.4%)	1 (0.5%)
Ear pruritus	2 (0.9%)	1 (0.5%)	1 (0.5%)
Tympanic membrane disorder	2 (0.9%)	0 (0.0%)	0 (0.0%)
Auricular swelling	1 (0.4%)	1 (0.5%)	0 (0.0%)
Balance disorder	1 (0.4%)	0 (0.0%)	0 (0.0%)

[1]Selected adverse reactions that occurred in ≥ 1 patient in the OTOVEL group derived from all reported adverse events that could be related to the study drug or the drug class.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ciprofloxacin and fluocinolone acetonide otic solution, 0.3% / 0.025% outside the US. 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.

- *Immune system disorders:* allergic reaction.
- *Infections and infestations:* candidiasis.
- *Nervous system disorders:* dysgeusia, paresthesia (tingling in ears), dizziness, headache.
- *Ear and labyrinth disorders:* ear discomfort, hypoacusis, tinnitus, ear congestion.
- *Vascular disorders:* flushing.
- *Skin and subcutaneous tissue disorders:* skin exfoliation.
- *Injury, poisoning and procedural complications:* device occlusion (tympanostomy tube obstruction).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

OTOVEL is negligibly absorbed following otic administration and maternal use is not expected to result in fetal exposure to ciprofloxacin and fluocinolone acetonide *[see Clinical Pharmacology (12.3)].*

8.2 Lactation

Risk Summary

OTOVEL is negligibly absorbed by the mother following otic administration and breastfeeding is not expected to result in exposure of the infant to ciprofloxacin and fluocinolone acetonide [*see Clinical Pharmacology (12.3)*].

8.4 Pediatric Use

OTOVEL has been studied in patients as young as 6 months in adequate and well-controlled clinical trials. No major differences in safety and effectiveness have been observed between adult and pediatric patients [*see Indications and Usage (1) and Dosage and Administration (2)].*

8.5 Geriatric Use

Clinical studies of OTOVEL did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

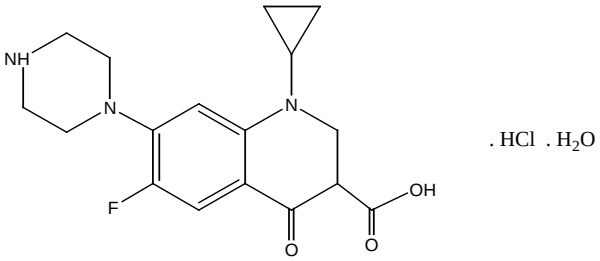
Due to the characteristics of this preparation, no toxic effects are to be expected with an otic overdose of OTOVEL.

11 DESCRIPTION

OTOVEL (ciprofloxacin and fluocinolone acetonide) otic solution, 0.3% / 0.025% is a sterile, preservative-free, clear otic solution containing the fluoroquinolone antibacterial, ciprofloxacin hydrochloride, combined with the corticosteroid, fluocinolone acetonide. Each single-dose vial contains a deliverable volume of 0.25 mL solution of ciprofloxacin hydrochloride equivalent to 0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide. The pH of the solution ranges from 3.5 to 5.0. The inactive ingredients are polysorbate 80, glycerin, povidone K90F and water for injection.

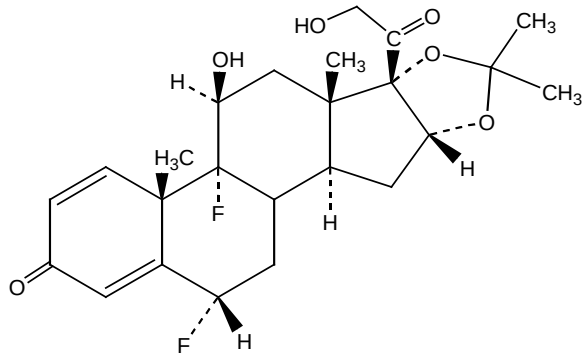
Ciprofloxacin is available as the monohydrochloride, monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its molecular formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.

The chemical structure of ciprofloxacin hydrochloride is:



The chemical name of fluocinolone acetonide is (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy- 16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone[67-73-2]. Its molecular formula is $C_{24}H_{30}F_2O_6$.

The chemical structure of fluocinolone acetonide is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ciprofloxacin is a fluoroquinolone antibacterial [*see Microbiology (12.4)*].

Fluocinolone acetonide, a corticosteroid, 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 A2, 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.

12.3 Pharmacokinetics

In two studies in children with AOMT aged ≥ 6 months to 12 years, blood samples were taken in subgroups of 16 and 14 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 concentrations of ciprofloxacin and/or fluocinolone acetonide following administration of OTOVEL otic solution at the recommended dosage regimen of 0.25 mL twice daily. Pharmacokinetic (PK) analysis resulted in only 1 sample showing a detectable concentration of ciprofloxacin in plasma of 3.0 mcg/L after 7 days of treatment, and no detectable concentrations in plasma of fluocinolone acetonide were observed. However, the sample with detectable ciprofloxacin concentrations was from a patient who had bilateral AOMT (protocol deviation because all patients participating in the PK study were to have unilateral otorrhea) and who received treatment in both ears with ciprofloxacin 0.3% otic solution, the active comparator.

12.4 Microbiology

Mechanism of Action

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

Resistance

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.

Antimicrobial Activity

Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and clinically in otic infections [*see Indications and Usage (1)*]:

Aerobic Bacteria:

Gram-positive Bacteria:
Staphylococcus aureus
Streptococcus pneumoniae

Gram-negative Bacteria:
Pseudomonas aeruginosa
Haemophilus influenzae
Moraxella catarrhalis

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long term studies of OTOVEL have been performed to evaluate carcinogenic potential. Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. Long-term animal studies have not been performed to evaluate the carcinogenic potential of fluocinolone acetonide.

Mutagenesis

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)

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

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

Studies have not been performed to evaluate the mutagenic potential of fluocinolone acetonide. Some corticosteroids have been found to be genotoxic.

Impairment of Fertility

No reproduction toxicity studies were conducted with OTOVEL. Absorption of ciprofloxacin and fluocinolone acetonide following otic administration of OTOVEL at the recommended dosage is negligible [*see Clinical Pharmacology (12.3)*].

14 CLINICAL STUDIES

Two phase 3 multicenter, randomized, double-blind, active-controlled, parallel group trials were conducted in 662 pediatric patients in total (aged 6 months to 12 years old) with AOMT, to assess the efficacy and safety of OTOVEL compared to ciprofloxacin otic solution and to fluocinolone acetonide otic solution (Trial 1 and Trial 2).

In both trials, the OTOVEL treatment arms showed significantly shorter times to cessation of otorrhea in comparison to both the ciprofloxacin and fluocinolone acetonide alone arms demonstrating the contribution of both components of OTOVEL. The results are presented in the table below:

Table 2: Results of the Primary Endpoint: Time to Cessation of Otorrhea (Trial 1 and Trial 2)

	Treatment arm		
Trial 1	**OTOVEL (N=112)**	**CIPRO (N=109)**	**FLUO (N=110)**
Number (%) with cessation of otorrhea by Day 22	88 (78.6%)	73 (67.0%)	53 (48.2%)
Median time to cessation* (days)	3.75	7.69	n.e.
p-value vs OTOVEL**		<0.001	<0.001
Trial 2	**OTOVEL (N=111)**	**CIPRO (N=112)**	**FLUO (N=108)**
Number (%) with cessation of otorrhea by Day 22	87 (78.4%)	77 (68.8%)	47 (43.5%)
Median time to cessation* (days)	4.94	6.83	n.e.
p-value vs OTOVEL**		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
* 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)

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied

OTOVEL (ciprofloxacin and flocinolone acetonide) otic solution, 0.3 %/0.025 %, is a sterile, preservative-free, clear otic solution supplied in blue translucent single-dose 0.25 mL vials. Fourteen single-dose vials are packaged in a protective foil pouch contained in a carton (NDC 24338-080-14).

Storage

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light; store unused vials in pouch and discard 7 days after opening the pouch. Do not open until ready to use. Discard vial after use.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (*Patient Information* and *Instructions for Use*).

Administration Instructions

- Advise patients that OTOVEL is for otic use only. It is not to be used in the eyes.
- Advise patients to warm the otic solution by holding the vial in the hand for 1 to 2 minutes before instilling it in the ear, to avoid dizziness.

Hypersensitivity Reactions

- Advise patients to immediately discontinue OTOVEL at the first appearance of a skin rash or any other sign of hypersensitivity *[see Warnings and Precautions (5.1)]*

OTOVEL is:

Distributed by:
Arbor Pharmaceuticals, LLC.
Atlanta, GA 30328

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