HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OTIPRIO safely and effectively. See full prescribing information for OTIPRIO.

OTIPRIO™ (ciprofloxacin otic suspension), for intratympanic use
Initial U.S. Approval: 1987

INDICATIONS AND USAGE

OTIPRIO is a fluoroquinolone antibacterial indicated for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement. (1)

DOSAGE AND ADMINISTRATION

- OTIPRIO is for intratympanic administration only. (2.1)
- OTIPRIO is intended for single-patient use with two 0.1 mL doses available in each vial. (2.1)
- Administer OTIPRIO as a single intratympanic administration of one 0.1 mL (6 mg) dose into each affected ear, following suctioning of the middle ear effusion. (2.1)
- See Full Prescribing Information for directions for OTIPRIO dose preparation. (2.2)

DOSAGE FORMS AND STRENGTHS

Otic Suspension: Each OTIPRIO vial contains 1 mL of 6% (60 mg/mL) ciprofloxacin otic suspension. (3)

CONTRAINDICATIONS

OTIPRIO is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to quinolones, or to any component of OTIPRIO. (4)

WARNINGS AND PRECAUTIONS

Potential for Microbial Overgrowth: OTIPRIO may result in overgrowth of non-susceptible bacteria and fungi. (5.1)

ADVERSE REACTIONS

The most frequently occurring adverse reactions (with an incidence rate greater than 3 %) were nasopharyngitis and irritability. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Otonomy at 1-800-826-6411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OTIPRIO is indicated for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Important Administration Instructions

- OTIPRIO is for intratympanic administration only.
- OTIPRIO is intended for single-patient use, discard unused portion.
- Administer OTIPRIO as a single intratympanic administration of one 0.1 mL (6 mg) dose into each affected ear, following suctioning of middle ear effusion.

2.2 Preparation of OTIPRIO

Directions for OTIPRIO dose preparation and handling is illustrated in Figure 1 below.

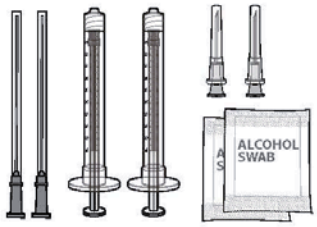
Figure 1: Directions for OTIPRIO Dose Preparation

STEP 1 Preparation

Materials needed:

1 vial of OTIPRIO (enough for 2 doses); Two 1 mL luer lock syringes; Two 18G-21G preparation needles; Two 20-24G, 2-3 inch **blunt, flexible** administration needles; Alcohol pads; Optional: ice pack and drape to keep OTIPRIO vial cold

Keep product cold during preparation. If OTIPRIO thickens during preparation, place the vial back in refrigeration.



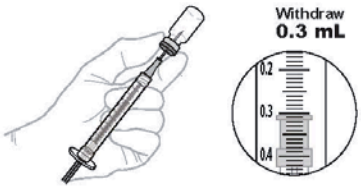
STEP 2 OTIPRIO Mixing

To keep the vial cold during shaking, hold the OTIPRIO vial by the aluminum seal to prevent gelation. **Shake the vial for 5 to 8 seconds** to mix well until a visually homogenous suspension is obtained.

Always hold the vial by the aluminum seal to prevent gelation.

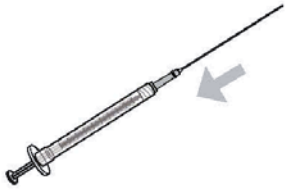
STEP 3 OTIPRIO Removal

Using an 18-21G needle, withdraw 0.3 mL of the suspension into the 1 mL syringe.



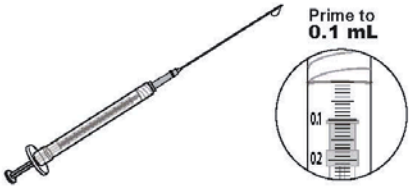
STEP 4 Replace with the Administration Needle

Replace the needle with a 20-24G, 2-3 inch **blunt**, flexible needle to be used for administration.



STEP 5 Priming the Syringe

Prime the needle leaving a dose of 0.1 ml (0.1 cc).



STEP 6 Preparing Second Dose for Bilateral Administration Only

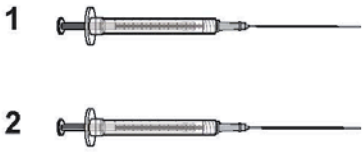
Repeat Steps 3, 4, and 5 using the same vial to prepare a second syringe for the other ear and dispose of the vial.

Use a different syringe for each ear.

After preparation, syringes can be kept at room temperature or in the refrigerator prior to administration.

Keep syringes on their side.

Discard syringes if not administered in 3 hours.



3 DOSAGE FORMS AND STRENGTHS

Otic Suspension: Each 1 mL of OTIPRIO contains a white, preservative-free, sterile otic suspension consisting of 6% (60 mg/mL) ciprofloxacin in a single-patient use glass vial.

4 CONTRAINDICATIONS

OTIPRIO is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components of OTIPRIO.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Microbial Overgrowth

OTIPRIO may result in overgrowth of nonsusceptible bacteria and fungi. If such infections occur, institute alternative therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

In two randomized, sham-controlled Phase 3 clinical trials, 530 pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement were treated with OTIPRIO or sham administered intra-operatively as a single dose. The median age of the pediatric patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age.

Adverse reactions that occurred in at least 3% of OTIPRIO patients and at an incidence greater than sham are presented in Table 1.

Table 1: Adverse Reactions in Phase 3 Trials

Adverse Reactions	**OTIPRIO (N=357)**	**Sham (N=173)**
Nasopharyngitis	5%	4%
Irritability	5%	3%
Rhinorrhea	3%	2%

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Animal reproduction studies have not been conducted with OTIPRIO. No adequate and well-controlled studies have been performed in pregnant women. Because of the negligible systemic exposure associated with clinical administration of OTIPRIO, this product is expected to be of minimal risk for maternal and fetal toxicity when administered to pregnant women**.**

8.2 Lactation

Risk Summary

Ciprofloxacin is excreted in human milk with systemic administration. However, because of the negligible systemic exposure after otic application, nursing infants of mothers receiving OTIPRIO should not be affected.

8.4 Pediatric Use

The safety and effectiveness of OTIPRIO in infants below six months of age have not been established.

The safety and effectiveness of OTIPRIO was established in 530 pediatric patients with bilateral otitis media with middle ear effusion undergoing myringotomy with tympanostomy tube placement. The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

11 DESCRIPTION

OTIPRIO (ciprofloxacin otic suspension) 6 % contains the synthetic fluoroquinolone antibacterial, ciprofloxacin. OTIPRIO is for intratympanic administration. OTIPRIO is supplied as a white, preservative-free, sterile otic suspension of 6% (w/v) ciprofloxacin in a neutral pH, buffered, isotonic solution in a single-patient use glass vial with a rubber stopper containing 1mL. The inactive ingredients are poloxamer 407, sodium chloride, tromethamine, hydrochloric acid and water for injection (WFI).

The thermosensitive suspension exists as a liquid at room temperature or below and gels when warmed *[see How Supplied/Storage and Handling (16)]*.

Ciprofloxacin has the following nomenclature:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.3.

Its chemical structure is as follows:

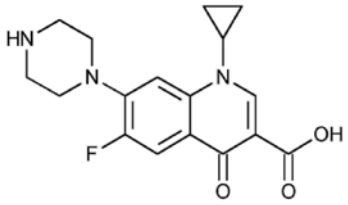


Figure 2: Structure of Ciprofloxacin

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

The plasma concentration of ciprofloxacin following bilateral administration of 0.1 mL OTIPRIO was not measured.

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 fluoroquinolones can develop through chromosomally- 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:

Gram-positive Bacteria

Staphylococcus aureus

Streptococcus pneumoniae

Gram-negative Bacteria

Haemophilus influenzae

Moraxella catarrhalis

Pseudomonas aeruginosa

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Salmonella/Microsome Test (Negative)

Escherichia 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 in vitro 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)

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg in mice and 250 mg/kg in rats (for mice and rats respectively, approximately 300 and 200 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 OTIPRIO) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be approximately 80 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 OTIPRIO.

13.2 Animal Toxicology and/or Pharmacology

Guinea pigs dosed in the middle ear with OTIPRIO exhibited no drug-related structural or functional changes of the cochlear hair cells.

14 CLINICAL STUDIES

Two randomized, multicenter, controlled clinical trials in 532 pediatric patients with bilateral otitis media with effusion undergoing myringotomy with tympanostomy tube placement evaluated the safety and efficacy of OTIPRIO when administered intra-operatively as a single

dose. The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age. The efficacy endpoint for both trials was the cumulative proportion of study treatment failures through Day 15, defined as the occurrence of any of the following events: otorrhea as determined by a blinded assessor on or after 3 days post-surgery, otic or systemic antibacterial drug use for any reason any time post-surgery, as well as patients who missed visits or were lost-to-follow-up. Table 2 presents the results from each Phase 3 trial.

Table 2: Cumulative Proportion of Treatment Failures Through Day 15 in Phase 3 Trials

	Trial 1 (N=266)			Trial 2 (N=266)		
	OTIPRIO	**Sham**	**Difference (Sham – OTIPRIO) (95% CI)**	**OTIPRIO**	**Sham**	**Difference (Sham – OTIPRIO) (95% CI)**
Treatment Failure	25% (44/179)	45% (39/87)	20% (8%, 32%)[2]	21% (38/178)	45% (40/88)	24% (12%, 36%)[2]
Reason for Failure[1]						
Otorrhea	7%	11%		7%	27%	
Otic antibacterial drugs	6%	17%		5%	8%	
Systemic antibacterial drugs	2%	5%		3%	3%	
Lost-to-follow-up and missed visit	10%	11%		6%	7%	

[1] the earliest occurring treatment failure event, and patients were classified as a treatment failure due only to that component for the remainder of the study

[2] P-value <0.001 for Cochran-Mantel-Haenszel test (adjusted for age-group)

Administration of OTIPRIO did not lead to impairment in hearing function, middle ear function or tube patency by Day 29.

16 HOW SUPPLIED/STORAGE AND HANDLING

OTIPRIO is a sterile, preservative-free, otic suspension of 6% (60 mg/mL, w/v) ciprofloxacin in a neutral pH buffered, isotonic solution containing poloxamer 407.

Each OTIPRIO carton contains 1mL of 6% (60 mg/mL, w/v) ciprofloxacin in a 2 mL single-patient use glass vial fitted with a rubber stopper. (NDC-69251-201-01)

OTIPRIO should be stored at 2 to 8ºC (36 to 46°F) until prior to use to prevent thickening during preparation. Protect from light. Store in the original carton until dose preparation.

17 PATIENT COUNSELING INFORMATION

Advise patients and their caregiver(s) that there may be drainage from the ear the first few days following ear tube surgery, but if the ear becomes painful, or continuous ear discharge is noted, or the patient develops a fever, advise patients and their caregiver(s) to consult their physician.

Distributed by:
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