

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207986Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	207986
Submission Date	02/25/2015
Drug	OTO-201 (Ciprofloxacin)
Trade Name	TBD
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Seong Jang, PhD
OCP Division	DCP4
OND Division	DAIP
Sponsor	Otonomy Inc.
Submission Type	505(b)(2)
Formulation	6% (b) (4) suspension
Indication	Treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement
Dosage and Administration	Single intratympanic administration of 0.1 mL into each affected ear.

1. EXECUTIVE SUMMARY

Otonomy submitted a 505(b)(2) application on 02/25/2015 that relies on FDA's prior findings of nonclinical safety for ciprofloxacin tablets (Cipro® Tablets - NDA 019537). OTO-201 is a formulation that allows for sustained exposure of the fluoroquinolone antibiotic ciprofloxacin to the middle ear, is administered directly to the middle ear via intratympanic injection. This formulation is a suspension of ciprofloxacin in a poloxamer 407 buffered solution. OTO-201 is intended for single-patient use with two 0.1 mL doses available in each vial.

At the concentration utilized in the OTO-201 formulation, the poloxamer 407 vehicle exhibits thermos-reversible properties: OTO-201 exists as a liquid at room temperature and gels after administration into the middle ear, as a result of the transition from room temperature to body temperature. In contrast, Ciprodex® and Cetraxal® are quickly drained from the middle ear, primarily via the Eustachian tube, and require frequent and repeated applications to maintain adequate concentrations of ciprofloxacin in the middle ear. OTO-201 will be administered as a single intratympanic application at the time of myringotomy and tympanic tube (TT) placement in pediatric subjects. OTO-201 allows for the sustained exposure of ciprofloxacin in the middle ear, providing a full course of therapy from a single application.

Otonomy completed two randomized, prospective, double-blind, sham-controlled Phase 3 clinical trials with identical protocols that enrolled a total of 532 pediatric patients at approximately 55 centers in the United States and Canada (Studies 201-201302 and 201-2013030). Results demonstrating that OTO-201 achieved the primary efficacy endpoint, a significant association between treatment and treatment failure, $p < 0.001$, favoring OTO-201

was observed for both trials (age-adjusted odds ratio (OR) of 0.388 and 0.299 for Studies 201-201302 and 201-201303, respectively). The adjusted relative risk (RR) (OTO-201 versus sham) of cumulative treatment failure for Studies 201- 201302 and 201-201303 was 0.548 and 0.463, respectively, indicating a reduction in the risk of treatment failure by approximately half for the OTO-201 group relative to sham. Overall, the safety evaluation from these studies also indicates that OTO-201 is safe and well tolerated. For additional details on the safety and efficacy aspects of the product please refer to the review by the Clinical Reviewer, Dr. Mark Needles.

Given that otitis media is a disease of the middle ear, delivery of antimicrobials to this otic compartment has been shown to be quite effective, with little to no consequent systemic exposure to this class of drugs and reducing the risk of bacterial resistance. Based on the characteristics of local delivery, bioavailability of the active pharmaceutical is mostly less of an issue compared to systemic exposure. However, given that the primary route of elimination of drugs from the middle ear is the Eustachian tube, drug residence time tends to be the biggest challenge for effectiveness. This is evident by the requirement for otic drops to be delivered multiples times daily in order to achieve sufficient middle ear drug concentrations. Otonomy has developed OTO-201 to overcome the challenges associated with drug clearance from the Eustachian tube. Pharmacokinetic studies in animals demonstrated that a single intratympanic injection of OTO-201 yields a middle and inner ear exposure profile comparable to that with a twice daily, 7-day regimen of Cetraxal or Ciprodex (total ciprofloxacin dose of 0.426 mg over 7 days). Furthermore, OTO-201 offers several important advantages over ciprofloxacin-containing ear drops: (1) stable exposure to ciprofloxacin, avoiding the fluctuating intermittent drug exposure encountered with ear drops, (2) maintenance of drug concentrations significantly above MIC, ensuring optimal clinical efficacy, and (3) the flexibility of varying the duration of middle ear exposure (a function of the dose) without impacting the antimicrobial efficacy. Additionally, OTO-201 has a middle ear nonclinical safety profile which is comparable or better to that of the approved dosage forms of Cetraxal and Ciprodex, since these marketed products appear to be associated with cochlear toxicity that is not observed with a single injection of OTO-201.

No clinical pharmacology studies have been conducted with OTO-201. The applicant did not submit any new clinical pharmacology information with this NDA. The label submitted by the applicant contained no new changes to the clinical pharmacology section.

2. RECOMMENDATIONS

No new clinical pharmacology was submitted by the applicant in this NDA and thus, the clinical pharmacology team has no additional comments on this submission and recommends approval of this 505(b)(2) NDA pending acceptable safety efficacy determination and label information.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAKSHINA M CHILUKURI
10/14/2015

SEONG H JANG
10/14/2015