CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207986Orig1s000

SUMMARY REVIEW

Division Director Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Memo
NDA # s	207986
Applicant Name	Otonomy Inc.
Date of Submission	February 25, 2015
PDUFA Goal Date	December 25, 2015
Established (USAN) Name	Ciprofloxacin otic suspension
Trade Name	OTIPRIO
Dosage Forms / Strength	Otic suspension/60 mg/mL
Proposed Indications	Treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Thomas Smith MD
Pharmacology Toxicology Review	James Wild PhD
Product Quality Review	Chunchun Zhang PhD
Medical Officer Review	Mark Needles MD
Statistical Review	Mushfiqur Rashid PhD
Microbiology Review	Jalal Sheikh PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Office of Scientific Investigations	John Lee MD
Division of Medication Error Prevention and Analysis	Sevan Kolejian Pharm D
Office of Prescription Drug Promotion	Adam George Pharm D

1.0 Introduction

Otonomy Inc. submitted NDA 207986 on February 25, 2015, for the use of ciprofloxacin 6% otic suspension (OTO-201) for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement. This application is covered under section 505(b)(2) of the Food Drug and Cosmetic Act and relies in part on the Agency's previous findings of safety and efficacy for ciprofloxacin tablets (NDA 19537). In this drug product, ciprofloxacin is suspended in a solution containing a thermosensitive mucoadhesive glycol polymer, polaxamer 407, that exists as a liquid at or below room temperature and as a gel when warmed. The drug is administered as a single intratympanic injection of 0.1 mL into each affected ear.

The clinical program, conducted under IND 110244, included one Phase 1b trial and two Phase 3 trials. The Phase 3 trials were identical, randomized, double-blind (patient and evaluator), sham-controlled trials in which patients were randomized 2:1 to receive either a single intratympanic dose of OTO-201 or a sham dose.

2.0 Background

Otitis media with effusion (OME) can develop following an episode of acute otitis media and can persist for months. It is generally asymptomatic and can be associated with conductive hearing loss. In most children, OME resolves within a few months without specific intervention, with most episodes that follow acute otitis media resolving within three months. However, 5-10% of episodes of OME last one year or longer. When OME persists and there is substantial hearing loss, tympanostomy tube placement is considered. There are no FDA-approved products for the treatment of OME.

The review team has completed their reviews of this application. For a detailed discussion of NDA 207986, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Application Technical Lead for NDA 207986 is Chunchun Zhang, PhD.

The drug substance, ciprofloxacin will be supplied by two suppliers and the Drug Master Files referenced ((b) (4)) have been previously reviewed and found to be adequate.

The drug product consists of ciprofloxacin otic suspension 6% (60 mg/mL, w/v) packaged in 2 mL, USP Type I glass vials with a 13 mm (b) (4) stopper, and a 13 mm aluminum seal with plastic flip-off top. The excipients used in the formulation are

compendial. No novel excipients are used in the formulation. The container closure system was found to be acceptable.

Eighteen months of stability data obtained at 5°C and 25°C/60% RH were provided for three primary registration batches, and twelve month data for batch W0007564 and six month data for batch 14239 were provided as supportive data. The only obvious trend noted was the higher (b) (4) content with time and temperature. However, all data provided are within the proposed limits and found to be acceptable. The proposed shelf life of 30 months is acceptable when stored between 2°C to 8°C (36°F to 46°F) in 2 mL glass vials, in the marketing package (cartons) protected from light. Photostability data suggests the drug product is photosensitive and should be protected from light. The marketing package (b) (4)) provides adequate protection for the proposed drug product from photo-degradation. The drug product was also found to be acceptable from a product quality microbiology perspective.

All facilities were found acceptable by the Office of Process and Facilities.

(b) (4)

I concur with the recommendations made by the product quality review team that from a product quality perspective, the data are adequate to support approval of the NDA.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is James Wild, PhD. Moderate hearing loss (changes in auditory brain stem responses (ABR) measured at three frequencies) was seen in one of the three studies in guinea pigs receiving a single intratympanic injection of 6% OTO-201. The hearing loss was not associated with microscopic evidence of cochlear damage. Hearing loss and cochlear damage were associated with 7-day intratympanic administrations of Ciprodex® and Cetraxal® in guinea pigs. Also, 6% OTO-201 produced a low incidence of ossicle immobility (4/20 ears in one study and 1/20 ears in another) which was similar to the effects of Cetraxal in the same studies (ossicle immobility in 2/20 ears in the first study and 3/20 ears in the second study). Other middle ear findings resulting from single-intratympanic administrations of OTO-201 were fluid granulomatous inflammation, fibroplasia, foamy macrophages, and foreign material which occurred in a dose-dependent manner with greater severity and incidence for 6% OTO-201 compared to saline. These findings were considered to be consistent with a foreign

body reaction. In a single intratympanic-dose study in rats with (b)(4)% poloxamer 407 (P407), similar findings largely resolved over time.

No consistent changes in systemic toxicity endpoints or laboratory measurements were seen. The vehicle for OTO-201, (b)(4)% P407, is a component of several approved products. However, the genotoxicity potential of P407 has not been reported. P407 rapidly forms a gel (b)(4) and this characteristic restricts easy evaluation of P407 in traditional genotoxicity assays. Dr. Wild notes that for the purposes of this NDA, the restricted systemic exposure, single-dose application, and prior use in previously approved products support the safety of P407 for genotoxicity.

(b)(4) produced as a result of an early (b)(4) technique for the vehicle, (b)(4)% P407, were associated with increased ABR values at three frequencies and cochlear toxicity (inner ear sensory hair loss). Hence, the (b)(4) technique for the (b)(4)% P407 vehicle was changed to a (b)(4) technique which substantially reduced the production of (b)(4). The acceptance criteria for each specific (b)(4) and the total (b)(4) will be determined by the highest (b)(4) levels at which no ototoxicity was seen in nonclinical toxicology studies.

Dr. Wild recommends approval of this NDA from a pharmacology/toxicology perspective. I agree with his assessment.

5.0 Clinical Microbiology

The clinical microbiology reviewer for this NDA is Jalal Sheikh, PhD.

The Applicant conducted an in vitro study of ciprofloxacin and other antibacterial drugs against isolates of the target pathogens recovered from otic and other respiratory infections from 2010 to 2012. Approximately half of the specimens were collected in the U.S., and most of the remaining specimens were collected in Europe and Asia. Ciprofloxacin was active against *Moraxella catarrhalis*, most isolates of *Streptococcus pneumoniae, Haemophilus influenzae* and methicillin-susceptible *Staphylococcus aureus*. Approximately 25% of *Pseudomonas aeruginosa* isolates tested were nonsusceptible.

The Applicant evaluated time-kill kinetics of ciprofloxacin against otic or respiratory isolates of the target pathogens at concentrations expected to be locally achievable following administration of OTO-201. Ciprofloxacin was bactericidal at concentrations of 4 to 8 times the minimum inhibitory concentrations (MICs) for most isolates tested.

The Applicant evaluated the activity of OTO-201 in a chinchilla model of otitis media with effusion due to *S. pneumoniae*. Following middle ear drainage and ventilation tube placement, a single intratympanic administration of various doses of OTO-201, reduced the recurrence of

otitis media at Day 6 compared to vehicle. A single intratympanic administration of OTO-201 at doses ranging from 0.06% to 6.0% reduced bacterial load and middle ear effusion.

In vitro surveillance data from 2008 to 2010 showed that resistance to ciprofloxacin and levofloxacin was infrequent among isolates of *S. pneumoniae* and *H. influenzae*. Data were limited for *M. catarrhalis*. However, data from the literature suggests that isolates of *M. catarrhalis* are 100% susceptible to ciprofloxacin. For both *P. aeruginosa* and *S. aureus* isolates, increased resistance to ciprofloxacin was observed.

Dr. Sheikh recommends approval of the NDA with labeling revisions. I agree with Dr. Sheikh's assessment.

6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Dakshina Chilukuri, PhD. The drug is intended for local administration, and plasma concentrations of ciprofloxacin were not measured. Dr. Chilukuri noted that pharmacokinetic studies in animals demonstrated that a single intratympanic injection of OTO-201 produced ciprofloxacin exposure profiles in the middle and inner ear that were comparable to the profiles observed with administration of a similar total doses of Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) and Cetraxal (ciprofloxacin 0.2%), administered twice daily for 7 days.

The proposed dose of OTO-201 is a single intratympanic administration of 0.1 mL (6 mg) to each affected ear following suctioning of the middle ear effusion during tympanostomy tube placement. This dose was selected following a dose-escalation study in which OTO-201 was administered in doses of 4 mg or 12 mg in 0.2 mL volume. Investigators reported difficulty administering a 0.2 mL volume and most were able to administer at least 0.1 mL. The Applicant therefore selected the 6 mg/0.1 mL dose for further development.

Dr. Chilukuri recommends approval of the NDA and I agree with his recommendation.

7.0 Clinical Efficacy and Safety

The clinical reviewer for this NDA is Mark Needles, MD and the statistical reviewer is Mushfiqur Rashid, PhD.

Efficacy

The Applicant conducted two identical Phase 3 trials (Study 201-201302 and Study 201-201303) to evaluate the safety and efficacy of a single intratympanic injection of OTO-201 for the treatment of otitis media with middle ear effusion in pediatric patients ages 6 months to 17 years requiring tympanostomy tube placement.

The two trials were identical in design and compared one dose of OTO-201 (6 mg) to sham (empty syringe with air). The two trials were conducted in parallel and enrolled patients at 29 centers in Study 201-201302 and 19 centers in Study 201-201303. Study sites were in the US or Canada. Patients with bilateral middle ear effusion confirmed via otoscopic exam were randomized to receive a single, intratympanic injection of 6 mg of OTO-201 or sham in each ear at the time of myringotomy and tympanostomy tube placement. On the day of surgery, the OTO-201 and sham syringes were prepared by a nurse or pharmacist and the syringes were covered to maintain the blind in the operating room. The treating otolaryngologist was unblinded at the time of administration because of the appearance of the treatment. Patients, their caregivers, and study site staff were blinded with respect to treatment administered. At the follow up visits, a blinded assessor performed an external ear examination to evaluate for the presence or absence of otorrhea.

A culture of the middle ear effusion was collected from each ear prior to intratympanic administration. Patients returned to the study site for follow-up assessments on Days 4, 8, 15 and 29 to assess for presence of otorrhea, tube patency, hearing function, and middle/external ear condition. Caregivers were encouraged to return for unscheduled visits if otorrhea was observed from any ear on or after three days post-surgery (Day 4), if the patients experienced an adverse event between scheduled visits, or if the patients required follow-up on any adverse event prior to the end of study visit (Day 29).

The primary efficacy endpoint was the cumulative proportion of study treatment failures through the Day 15 visit.

A study treatment failure was defined as the first occurrence of any of the following components:

1. Otorrhea treatment failure – patient with otorrhea observed by the blinded assessor on or after the third day post-surgery (on or after Day 4) through the Day 15 visit.

2. Otic treatment failure – patient given an otic antibiotic any time post-surgery and either prior to or without confirmation of otorrhea by the blinded assessor through the Day 15 visit.

3. Systemic antibiotic treatment failure – patient given a systemic antibiotic any time post-surgery and either prior to or without confirmation of otorrhea by the blinded assessor through the Day 15 visit.

4. Lost to follow up treatment failure – patient at the scheduled Day 15 visit with an unknown study treatment failure status due to being lost to follow up.

5. Missed visit treatment failure – patient, not lost to follow up, who at a particular visit through the Day 15 visit had a missing treatment failure status because he/she did not

return to the clinic for a blinded assessment within the analytic time window and had not yet been identified as a study treatment failure.

Several secondary endpoints were also evaluated, including, cumulative proportion of study treatment failures through the Day 4 visit (Visit 3), cumulative proportion of study treatment failures through the Day 8 visit (Visit 4), cumulative proportion of study treatment failures through the Day 29 visit (Visit 6), time-to-study treatment failure through the Day 15 visit (Visit 5), cumulative proportion of otorrhea-only treatment failures as described above through the Day 15 visit (Visit 5), and microbiological response through the Day 15 visit (Visit 5) and Day 29 visit (Visit 6).

The frequency and percentage of patients who were study treatment failures through the Day 15 visit in the OTO-201 and sham groups were compared using a Cochran-Mantel-Haenszel (CMH) test stratified by the two age strata (6 months to 2 years and greater than 2 years). The CMH test was conducted at a two-tailed Type I error rate of 0.05. Overall risk differences for each age stratum were presented with their associated 95% confidence intervals (CI).

The analysis populations were defined as follows:

- Full Analysis Set (FAS): The FAS consisted of the Intent-to-Treat (ITT) population, where all randomized patients were analyzed in the group to which they were randomized regardless of the actual treatment received. The FAS was used for the efficacy analysis unless otherwise noted.

- Per-Protocol Set: The per-protocol population was a subset of the ITT population that included all randomized patients without major protocol deviations who had external ear examinations for otorrhea conducted by the blinded assessor at Days 4, 8, and 15 (Visits 3, 4, and 5, respectively).

- Microbiologically Evaluable Set (MES): The MES was a subset of the FAS that consisted of patients who had a baseline bacteriology sample positive for either *P. aeruginosa, S. aureus, S. pneumoniae, H. influenzae,* or *M. catarrhalis* in at least one ear.

- Safety Analysis Set: The safety analysis set included all patients who received actual treatment with either OTO-201 or sham. Patients were analyzed in the group to which they received actual treatment regardless of their randomized assignment.

In each trial, 266 patients were enrolled and randomized to receive either OTO-201 or sham using a 2:1 ratio stratified by age (6 months to 2 years or >2 years). Only patients with bilateral effusion confirmed on the day of surgery were randomized prior to surgery. Patients without bilateral effusion were not randomized and were considered screen failures.

In Study 201-201302, 160 males (60.2%) and 106 females (39.8%) were enrolled and in Study 201-201303, 144 males (54.1%) and 122 females (45.9%) were enrolled. The mean age was 2.4 years (range 0.5 to 12.6 years) and 2.5 years (range 0.5 to 11.6 years) in Studies 201-201302 and 201-201303, respectively. Patients ages 6 months to 2 years accounted for ~61% of the total population.

Dr. Rashid's analysis of the primary endpoint in the FAS and PP sets was consistent with the Applicant's analysis and is summarized in the following table:

Table 1: Cumulative Proportion of Treatment Failures through Day 15 in Phase 3 Trials (FAS and PP Set)

	Study 201-201302 (N=266)			Study 201-201303 (N=266)		
Population	**OTO-201**	**Sham**	**% Difference (Sham – OTO-201) (95% CI[3])**	**OTO-201**	**Sham**	**% Difference (Sham – OTO-201) (95% CI[3])**
Intent to Treat[1]	25% (44/179)	45% (39/87)	20% (8%, 32%)[3]	21% (38/178)	45% (40/88)	24% (12%, 36%)*
Per Protocol[2]	12% (18/148)	39% (27/70)	27% (14%, 39%)[3]	17% (27/159)	39% (29/74)	22% (10%, 35%)*

Modified from Table 2, CDTL Memo
[1]Intent to Treat population: All randomized patients
[2]Per Protocol population: Randomized patients compliant with protocol; excludes patients with out of window/missed visits or lost to follow-up
[3] All % differences and the corresponding 95% CIs were not adjusted for age strata
*p-value <0.001 for Cochran-Mantel-Haenszel test (adjusted for age-group)

In both trials, treatment failure at Day 15 in the overall population was significantly lower in OTO-201-treated group than the sham-treated group. A stronger treatment effect was seen in the younger age group stratum (6 months-2 years) and reached statistical significance in both trials. In the older age stratum (> 2 years), a treatment effect favoring the OTO-201 arm was seen in both trials; however, the effect was greater in Study 201-201302. In both trials, a greater proportion of patients in the sham group were identified as study treatment failure due to otorrhea-only, otic antibiotics-only, systemic antibiotics-only, or missed visit-only through all of the time points compared to the OTO-201 group. The proportion of patients identified as treatment failure due to lost to follow up-only through all the time points was comparable between the two treatment groups. For treatment failure due to otorrhea only, although the treatment effect favored OTO-201 in both trials, the results were stronger in Study 201-201303. It is important to note that the trials were not powered for testing the difference in treatment failures (at any visit) by the various components.

Dr. Rashid conducted additional sensitivity analyses that showed statistically significant differences favoring OTO-201 treatment when assuming patients prescribed systemic

antibacterial drugs were non-treatment failures or assuming patients with missing observations due to being lost to follow up or missed visits were non-treatment failures.

Analyses of secondary endpoints of treatment failures through Days 4, 8, and 29 showed results consistent with the primary analysis. In both trials, the time-to-treatment failure was significantly different between OTO-201 and sham groups using a log-rank test adjusted for age.

Patients with positive baseline cultures in at least one ear had a higher failure rate than patients with negative cultures in both ears regardless of treatment. In both culture positive and culture negative subgroups, failure rates were lower in the OTO-201 arm compared to the sham arm. The most frequently identified organisms were *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.

Dr. Rashid noted a treatment by gender interaction in Study 201-201302 with a substantial treatment benefit in male patients and little to no treatment effect in females and a treatment by age-group interaction in Study 201-201303 (higher treatment failure in the age Group: 6 months through 2 years). These findings did not affect his overall conclusions.

Safety

The following table summarizes the safety database across the Phase 1 trial and the two Phase 3 trials.

Table 2: Summary of Safety Database

Treatment	Number of Subjects
OTO-201[a] (any dose)	397
OTO-201 4 mg	21
OTO-201 6 mg	357
OTO-201 12 mg	19
Placebo (vehicle only)	22
Sham[b] (air injection)	194

Modified from Table 7.2.1-1, Clinical Review

[a] of the 397 patients randomized to OTO-201, 2 were not treated and 1 received sham; 3 patients randomized to sham were treated with OTO-201

[b] of the 196 patients randomized to sham, 3 were treated with OTO-201; 1 patient randomized to OTO-201 was treated with sham

No deaths were reported in any of the trials. Four Serious Adverse Events (SAEs) were reported in the Phase 1b and Phase 3 trials. In Study 201-201101, one patient in the 4 mg OTO-201 group experienced an SAE of chemical poisoning, from ingesting a dishwashing detergent tablet. In Study 201-201302, three patients in the OTO-201 group experienced three SAEs, one had gastroenteritis and two had bronchiolitis. No SAEs were reported in Study 201-201303.

Table 3 summarizes the common TEAEs reported in the Phase 3 trials and experienced by at least 3% of patients in the OTO-201 arm.

Table 3: Treatment-Emergent Adverse Reactions in Phase 3 Trials

Preferred term	OTO-201 N=357	Sham N=173
Pyrexia	40 (11.2%)	20 (11.6%)
Teething	24 (6.7%)	8 (4.6%)
Upper Respiratory Tract Infection	23 (6.4%)	12 (6.9%)
Procedural Pain	19 (5.3%)	15 (8.7%)
Nasopharyngitis	18 (5.0%)	6 (3.5%)
Cough	17 (4.8%)	11 (6.4%)
Irritability	17 (4.8%)	5 (2.9%)
Ear Pain	14 (3.9%)	6 (3.5%)
Nasal congestion	12 (3.4%)	5 (2.9%)
Rhinorrhea	12 (3.4%)	3 (1.7%)
Vomiting	11 (3.1%)	5 (2.9%)

Modified from Table 7.4.1-2, Clinical Review

In the Phase 1b study, treatment emergent adverse events reported by two or more patients in any treatment group and more frequently in the OTO-201 group (4 mg or 12 mg dose) were pyrexia, upper respiratory tract infection, diarrhea, and cough.

A greater proportion of patients in the OTO-201 group had at least one tympanostomy tube blocked at the Day 4 Visit compared to the sham group. At the Day 29 visit, at least one tube was obstructed in 18/354 (5%) OTO-201-treated patients and 7/171 (4%) sham-treated patients and at least one tube had extruded in 3/354 (1%) OTO-201-treated patients and 1/171 (1%) sham-treated patients.

Audiometry assessments were conducted in the Phase 1b and Phase 3 trials. All patients in the Phase 1b study underwent audiometry assessments appropriate for their age and developmental abilities. No safety concerns with regard to possible hearing loss were noted in the Phase 1b study. In the Phase 3 trials, audiometry assessments were not required in patients <4 years of age if they were non-cooperative with the audiometry testing at the screening visit. In the Phase 3 trials, results of air conduction were normal in the majority of ears or their results had shifted to normal by the Day 29 Visit. Except for one patient in the sham arm, bone conduction was normal at all visits. Shifts in pure tone average (PTA) indicating worsening of hearing were infrequent in either arm in both Phase 3 trials. On otoscopic examination, an effusion was often observed in the few patients with shifts in PTA.

The review team concludes that in each Phase 3 trial, the cumulative proportion of treatment failures were lower in patients who received OTO-201 compared with those receiving sham. The adverse events associated with OTO-201 were generally minor and self-limited, and there were no significant effects of the drug on otoscopic examinations, tympanometry, and audiometry. Drs. Needles and Rashid recommend approval of NDA 207986. Dr. Smith, the CDTL, also recommends approval of the NDA. I agree with their assessment.

8.0 Labeling

Labeling recommendation from Sevan Kolejian, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) and Adam George, PharmD, from the Office of Prescription Drug Promotion (OPDP) have been incorporated in labeling. The proposed proprietary name of OTIPRIO was found acceptable. Dr. Kolejian also reviewed the Human Factors protocol and the Instructions for Use (IFU) from a medication error perspective and found them acceptable.

9.0 Pediatrics

The Applicant requested a partial waiver of pediatric studies in children less than 6 months of age because studies are impossible or highly impracticable. The partial waiver request and the pediatric assessment were presented to the Pediatric Review Committee (PeRC) on November 18, 2015, and PeRC concurred with the Division's plan to grant the partial waiver.

10.0 Other Regulatory Issues

Clinical Site Inspections

John Lee, MD, from the Office of Scientific Investigations provided the clinical inspections summary for this NDA. Four clinical investigator sites were inspected based on large enrollment. One study site enrolled patients in both trials. At each of the four sites, subject case records were reviewed for nearly all enrolled subjects, including detailed review for 62 subjects. At Site 080 in Study 302 (Evans), a Form FDA 483 was issued for minor isolated discrepancies between source records and eCRF and repeatedly not reporting to the Sponsor the use of concomitant medications. The unreported medications included antibacterial drugs. Dr. Lee notes that this would not have a significant impact on the overall study outcome given the limited amount of affected data. Dr. Lee concluded that overall, the study conduct appeared adequate at all four sites, including the Sponsor's oversight of study conduct. All audited study data were adequately verifiable and appear reliable as reported in the NDA.

Advisory Committee Meeting

This NDA was not discussed at an Advisory Committee meeting.

11.0 Risk Management

Safety information is adequately included in labeling. There are no postmarketing commitments or requirements at this time.

12.0 Recommended Regulatory Action

The efficacy of OTO-201 for the treatment of pediatric patients (six months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement was demonstrated in two adequate and well-controlled trials. In both trials, cumulative failure rates were significantly lower in OTO-201-treated arm compared to the sham-treated arm. The adverse reactions noted in these trials were generally mild and self-limited and are adequately described in labeling.

In summary, I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of OTO-201 for the treatment of pediatric patients (six months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement. I recommend approval of NDA 207986.

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/s/

SUMATHI NAMBIAR
12/10/2015