# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208251Orig1s000

# SUMMARY REVIEW

# Division Director Decisional Memo

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Sumathi Nambiar MD MPH |
| **NDA** | 208251 |
| **Applicant Name** | Laboratorios SALVAT, S.A. |
| **Date of Submission** | June 30, 2015 |
| **PDUFA Goal Date** | April 30, 2016 |
| **Trade Name** | Otovel |
| **Dosage Forms / Strength** | Otic Solution (0.3 % ciprofloxacin and 0.025 % fluocinolone acetonide) |
| **Proposed Indications/Population** | Acute Otitis Media with Tympanostomy Tubes/Pediatric Patients 6 months and older |
| **Regulatory Action** | Approval |

| **Material Reviewed/Consulted**<br>Action Package including: | **Names of Discipline Reviewers** |
|---|---|
| Cross-Discipline Team Leader Review | Dmitri Iarikov MD PhD |
| Pharmacology Toxicology Review | Amy Ellis PhD |
| Product Quality Application Technical Lead | Dorota Matecka PhD |
| Medical Officer Review | Mayurika Ghosh MD |
| Statistical Review | Christopher Kadoorie PhD |
| Microbiology Review | Kalavati Suvarna PhD |
| Clinical Pharmacology Review | Dakshina Chilukuri PhD |
| Office of Scientific Investigations | John Lee MD |
| Division of Medication Error Prevention and Analysis | Sevan Kolejian PharmD |
| Labeling Reviews | Adam George PharmD<br>Nyedra Booker PharmD MPH |

## 1.0 Introduction

NDA 208251, ciprofloxacin and fluocinolone acetonide, was submitted by Laboratorios SALVAT, S.A on June 30, 2015. The Applicant submitted the NDA seeking the following (b) (4) indications:

1. Acute otitis media in pediatric patients (aged 6 months and older) with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

(b)(4)

This application is covered under Section 505(b)(2) of the Food Drug and Cosmetic Act, relying in part on the Agency's finding of safety and effectiveness of Cipro HC Otic (NDA 20805), as communicated by the Applicant on April 25, 2016.

The review team has completed their reviews of this application. For a detailed discussion of NDA 208251, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

## 2.0 Background

Tympanostomy tube placement is a commonly performed procedure in children. About 2/3$^{rds}$ of children with tympanostomy tubes develop episodes of acute otorrhea in the year following tube placement.[1] Otorrhea is generally considered a sign of an acute middle ear infection. The common bacteria associated with otorrhea include *S. pneumoniae*, *H. influenz*ae, *M. catarrhalis*, *S. aureus* and *P. aeruginosa*.[2]

Ciprofloxacin is a fluoroquinolone antibacterial drug with activity against several bacteria including *S. aureus, S. pneumoniae, H. influenzae, M. catarrhalis,* and *P. aeruginosa*. Fluocinolone acetonide is a corticosteroid used to decrease local inflammation. Approved otic ciprofloxacin products include Cetraxal (ciprofloxacin hydrochloride 0.2% otic solution), Cipro HC Otic (ciprofloxacin hydrochloride 0.2% and hydrocortisone 1% otic suspension), and Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension). Ciprodex is approved

[1] van Dongen TM, van der Heijden GJ et al. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. PLoS One. 2013;8(7)

[2] van Dongen TM, Venekamp RP, Wensing AM et al. Acute otorrhea in children with tympanostomy tubes: prevalence of bacteria and viruses in the post-pneumococcal conjugate vaccine era. Pediatr Infect Dis J. 2015;34(4):355-60.

for treatment of AOMT in pediatric patients 6 months and older and for treatment of AOE in pediatric patients 6 months and older and adults. Cetraxal and Cipro HC are approved for the treatment of AOE in pediatric and adult patients. There are approved fluocinolone containing topical products; none are approved for AOMT. (b) (4)

To support the AOMT indication, the Applicant provided data from two Phase 3 trials comparing ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution with ciprofloxacin 0.3% and with fluocinolone acetonide 0.025% otic solutions. (b)(4)

(b) (4)

(b) (4)

1. NDA 208251/Original-1 – Acute Otitis Media in pediatric patients (aged 6 months and older) with Tympanostomy Tubes

(b)(4)

(b)(4)

**3.0 Product Quality**

The proposed drug product contains two drug substances, ciprofloxacin hydrochloride and fluocinolone acetonide. Ciprofloxacin hydrochloride drug substance will be supplied by (b)(4) (b)(4) (holder of DMF (b)(4)), and fluocinolone acetonide will be supplied by (b)(4) (b)(4) (holder of DMF (b)(4)). Both DMFs were previously reviewed and found to be adequate. The excipients in the proposed formulation include polysorbate 80, glycerin, povidone K90F, and water for injection. All excipients used in the drug product manufacture are compendial (USP/NF).

The drug product container closure system is a low-density polyethylene (LDPE) translucent blue single-dose vial with a deliverable volume of approximately 0.25 mL. The vials (14-count) are contained in an aluminum foil overwrap pouch and a carton box for protection. Each vial contains one dose (0.25 mL solution) of approximately 0.75 mg of ciprofloxacin and 0.0625 mg

of fluocinolone acetonide. The proposed container closure system (LDPE vial) was evaluated for potential leachables. Leachables were tested on the drug product samples stored under long-term and accelerated conditions over time to demonstrate that throughout the proposed expiration period of the drug product, no leachables from the container and no inks from the pouch migrate into the drug product solution at levels above the specification limits.

Stability information submitted in the NDA support 24 months of expiration dating for the proposed drug product stored at 20°- 25°C (68° - 77°F) with excursions permitted to 15° to 30°C (59° to 86°F). The proposed storage time of 7 days after opening the pouch is also acceptable.

A low yield of the filling and overall manufacturing process was noted and this has not been completely addressed. To further demonstrate the robustness of the commercial process, the Applicant has agreed to provide the results from the drug product validation batches that will include actual yields for all unit operations and batch records, along with results from all in-process tests. This will be included as a postmarketing commitment.

The product quality review team has concluded that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product, ciprofloxacin and fluocinolone acetonide otic solution. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "approve" recommendation was provided by the Office of Process and Facilities.

The product quality review team recommends approval of the NDA. I concur with the recommendations made by the product quality review team.

## 4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is Amy Ellis, PhD.

There was no evidence of cochlear hair cell loss in guinea pigs dosed intratympanically with Otovel or vehicle twice daily for 28 days. Mild to moderate hearing loss was seen in female guinea pigs administered Otovel, as measured using Auditory Brainstem Response (ABR). Dr. Ellis notes that it is unusual that only females appeared to be affected and it is possible that the change was procedure-related. Previous studies with 0.3% ciprofloxacin have shown that this level was not toxic to cochlear hair cells when administered intratympanically to guinea pigs, although some otic products containing ciprofloxacin have been associated with inflammation of middle ear tissues which can affect hearing. Fluocinolone has not been previously studied for ototoxicity following intratympanic administration, but other corticosteroids, such as hydrocortisone and dexamethasone, did not appear to be ototoxic when given by this route. Results of a local lymph node assay (LLNA) conducted in mice suggest that

Otovel has a low potential for sensitization. When applied for up to 4 hours under semi-occlusive patches, neither Otovel nor its vehicle was an acute irritant to New Zealand White Rabbit skin.

Dr. Ellis notes that the quantity of Otovel that reaches the middle ear during clinical use is not likely to be at the level seen in the guinea pigs in the ototoxicity study. There are anatomical differences between the middle/inner ears of guinea pigs and humans (e.g., morphology of the round window membrane) that may contribute to the greater sensitivity of guinea pigs to compounds that are administered intratympanically. Additionally, the dosing procedure used in the guinea pig studies maximizes middle ear (and likely inner ear) exposure to the test compounds and the length of daily exposure in the animal study (28 days) exceeded the duration of treatment proposed for clinical use. Thus, Dr. Ellis considers Otovel to be reasonably safe for its intended use in humans.

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

## 5.0 Clinical Microbiology

The clinical microbiology reviewer for this NDA is Kalavati Suvarna, PhD.

The in vivo activity of topical ciprofloxacin hydrochloride was evaluated in a chronic suppurative otitis media model in cynomolgus macaques. The ear was inoculated progressively with increasing colony forming units of *P. aeruginosa* over 2 weeks. The monkeys were treated twice daily for 4 weeks with saline, vehicle, Cortisporin otic suspension (positive control), or Ciprofloxacin 0.2%. Three weeks post-therapy, *P. aeruginosa* was eradicated from all ears (10 of 10) in the ciprofloxacin and Cortisporin groups, 2 of 10 ears in the saline group, and 9 of 10 ears in the vehicle group. Eradication did not correlate with clearance of drainage.

A surveillance study was conducted to assess the in vitro activity of ciprofloxacin against recent bacterial isolates (2012 to 2014) associated with [redacted] (b)(4) otitis media. The ciprofloxacin minimum inhibitory concentrations for methicillin resistant *S. aureus*, methicillin-susceptible *S. aureus*, *P. aeruginosa*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were much below the concentration of ciprofloxacin in the otic solution (3000 mcg/mL).

Dr. Suvarna notes that in the two AOMT clinical trials, favorable microbiologic response was seen against isolates of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus* and *P. aeruginosa*. Efficacy results are discussed in Section 6.0 of this review.

As this is a topical product, susceptibility test interpretive criteria are not applicable.

Dr. Suvarna recommends approval of the NDA. I agree with her assessment.

## 6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Dakshina Chilukuri, PhD. Pharmacokinetic (PK) analysis was conducted in a subgroup of 14 patients from Study CIFLOTIII/10IA04 and 16 patients from Study CIFLOTIII/10IA02. Blood samples for PK assessment were collected before the administration of the first dose of Otovel on Day 1 and within 1 to 2 hours after the last dose on Day 7. Analysis of plasma samples was performed using a validated LC/MS/MS method with a limit of quantification for ciprofloxacin and/or fluocinolone acetonide of 1 ng/mL. In Study CIFLOTIII/10IA02, there was detectable concentration of ciprofloxacin in plasma (3 mcg/L) after 7 days of treatment in one sample (patient received twice the dose due to bilateral AOMT). There were no detectable concentrations of fluocinolone acetonide. The patient did not report any treatment-emergent adverse events (TEAE). In Study CIFLOTIII/10IA04, no detectable concentrations of fluocinolone acetonide in plasma were observed after 7 days of treatment, and no ciprofloxacin results were reported.

Dr. Chilukuri notes that even if 100% of a 3 mg otic dose is absorbed systemically, the expected $C_{max}$ for ciprofloxacin would be 31.5 ng/mL, approximately 67-fold less than 2.1 mcg/mL seen with an intravenous dose of ciprofloxacin 200 mg. Dr. Chilukuri notes that while the concentrations of both ciprofloxacin and fluocinolone acetonide in the majority of patients were below the limit of assay quantitation, information provided in the NDA is acceptable.

Dr. Chilukuri recommends approval of the NDA, pending agreement on labeling. I agree with his recommendation.

## 7.0 Clinical Efficacy and Safety

The clinical reviewer for this NDA is Mayurika Ghosh, MD and the statistical reviewer is Christopher Kadoorie, PhD.

### Efficacy

The Applicant conducted two randomized, double-blind, multi-center, superiority trials (Studies CIFLOTIII/10A02 and CIFLOTIII/10A04) in AOMT, referred to as Studies 02 & 04 respectively. Each trial included three treatment arms to establish the contribution of ciprofloxacin and fluocinolone to the combination product. The primary endpoint was time to cessation of otorrhea and the key secondary endpoint was sustained microbiological cure in the clinical intent-to-treat (CITT) population. The CITT population was defined as all patients who were randomly assigned to study medication.

The trials were similar in design with some differences such as the location of the sites, the time period in which they were conducted and the sample sizes of the individual treatment arms.

Study 02 was conducted from July 2011 to June 2014 in 46 sites (33 in the United States, 6 in South Africa, 3 in Spain, 1 in the Czech Republic, 1 in Denmark, 1 in Finland, and 1 in Sweden). This trial included a total of 331 randomized subjects (112 in the CIPRO+FLUO arm, 109 in the CIPRO arm and 110 in the FLUO arm).

Study 04 was conducted in 49 sites (35 in the United States, 6 in South Africa, 5 in Spain, 2 in Canada, and 1 in Finland). This trial also included a total 331 subjects (111 in the CIPRO+FLUO arm, 112 in the CIPRO arm and 108 in the FLUO arm).

Fifteen sites that completed participation in Study 02 also enrolled patients in Study 04. Study medication was administered to the affected ear(s) twice daily for 7 days. Enrollment was stratified by age (patients < 3 years old and patients ≥ 3 years).

Patients were mostly male (~60%) and White/Caucasian (~78%). The mean (median) age of the study population was 3.4 (2.6) years and 3.2 (2.4) years, in Studies 02 and 04, respectively. Demographic and baseline characteristics were generally balanced between the treatment arms.

In Study 02, the median number of days to cessation of otorrhea was 3.8 days in the CIPRO+FLUO arm and 7.7 days in the FLUO arm. In Study 04, the median number of days to cessation of otorrhea was 4.9 days for the CIPRO+FLUO arm and 6.8 days for the CIPRO arm. The median number of days was not estimable in the FLUO arm in either trial as the majority (51.8% & 56.5%) of patients were censored. Using the log rank test, superiority of CIPRO+FLUO vs. CIPRO (p-value < 0.001 in Trial 02, p-value = 0.028 in Trial 04) and the superiority of CIPRO+FLUO vs. FLUO (p-value < 0.001 in both trials) was demonstrated.

**Table 1: Primary Analysis: Time to Cessation of Otorrhea (CITT Population)**

| **Study 02** | **CIPRO+FLUO (N = 112)** | **CIPRO (N = 109)** | **FLUO (N = 110)** |
|---|---|---|---|
| Number (%) of patients with cessation of otorrhea | 88 (78.6%) | 73 (67.0%) | 53 (48.2%) |
| Number (%) of patients censored at Day 22 (no cessation of otorrhea) | 24 (21.4%) | 36 (33.0%) | 57 (51.8%) |
| Time to cessation of otorrhea (days)<br>Mean (SE)<br>Median (95% CI) | <br>6.9 (0.61)<br>3.8 (3.0, 4.4) | <br>10.8 (0.78)<br>7.7 (4.8, 11.4) | <br>12.6 (0.77)<br>NE (7.4, NE) |
| Log rank test p-value[1] | | < 0.001 | < 0.001 |
| **Study 04** | **CIPRO+FLUO (N = 111)** | **CIPRO (N = 112)** | **FLUO (N = 108)** |
| Number of patients with cessation of otorrhea | 87 (78.4%) | 77 (68.8%) | 47 (43.5%) |
| Number of patients censored (no cessation of otorrhea) | 24 (21.6%) | 35 (31.3%) | 61 (56.5%) |
| Time to cessation of otorrhea (days)<br>Mean (SE)<br>Median (95% CI) | <br>7.6 (0.63)<br>4.9 (3.7, 5.5) | <br>10.5 (0.78)<br>6.8 (5.5, 7.7) | <br>13.7 (0.70)<br>NE (13.9, NE) |
| Log rank test p-value[1] | | 0.028 | < 0.001 |

Source: Statistics Review, Table 5; [1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

Figures 1 and 2 show the cumulative percentage of patients in each treatment arm achieving cessation of otorrhea over the study period (22 days). The difference in cessation rates between CIPRO+FLUO and the other arms appeared to be substantial throughout most of the trials. Patients tended to achieve cessation within the first 10 days with only a few subjects achieving cessation after 10 days.

**Figure 1: Cessation of Otorrhea Over Time (Study 02)**

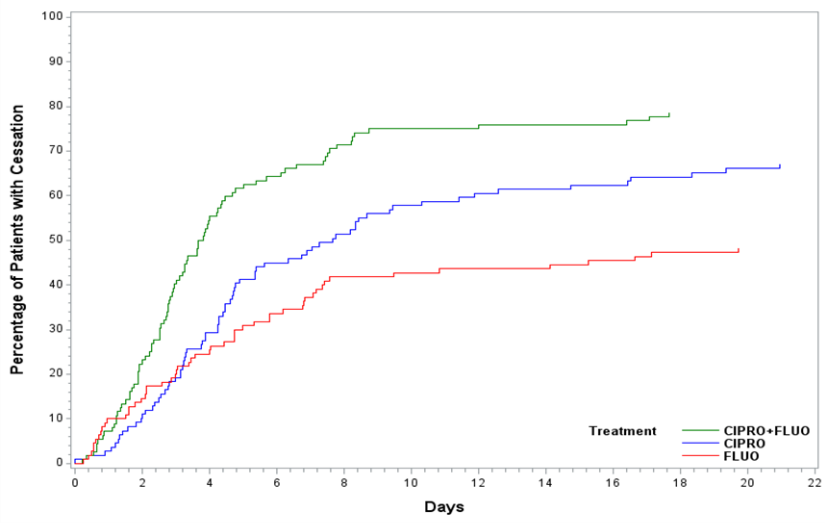
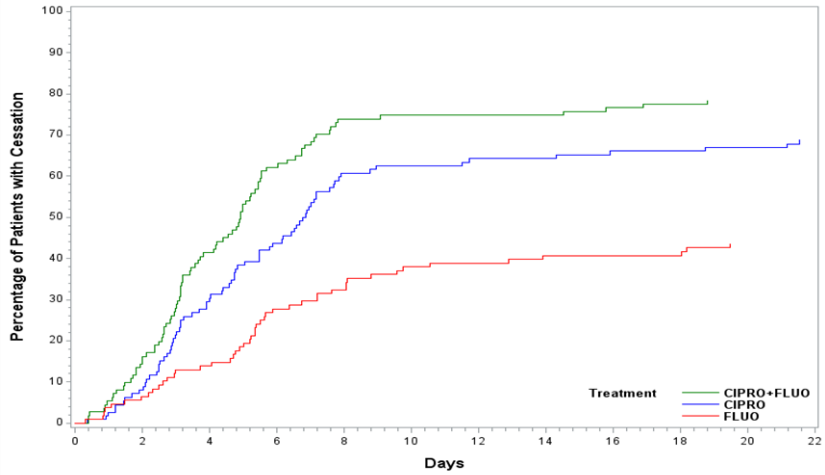



**Figure 2: Cessation of Otorrhea Over Time (Study 04)**




Source: Statistics Review

The key secondary analysis considered by the Applicant was sustained microbiological cure, defined as Eradication or Presumed Eradication in the per-patient microbiological response at both Visit 3 and Visit 4. The primary analysis of sustained microbiological cure was performed in the microbiological ITT population (CITT patients who had a baseline microbiological culture that yielded one or more pathogens from ear discharge).

In Study 02, pairwise comparisons of the CMH test, stratified by age showed a statistically significant difference in sustained microbiological cure between the CIPRO+FLUO group

compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p = 0.017$). In Study 04, pairwise comparisons showed a significant difference in sustained microbiological cure between the CIPRO+FLUO group compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p < 0.001$).

Dr. Kadoorie conducted several exploratory analyses of the primary endpoint in the CITT population under a variety of different assumptions. Generally, these analyses were supportive of findings reported for the primary analysis. Dr. Kadoorie also performed sensitivity analyses to assess the influence of sharing study sites on the findings of the primary analysis. Treatment comparisons did not meaningfully change when all shared sites were excluded.

Overall, in Dr. Kadoorie's assessment, the Applicant has provided adequate evidence of efficacy and safety to support the use of Otovel in the treatment of pediatric patients 6 months and older with AOMT. In addition to meeting primary and secondary study objectives, sensitivity analyses demonstrated that the findings for efficacy were robust across a variety of assumptions.

**Safety**

In the two Phase 3 AOMT trials, a total of 224 patients received Otovel, 220 received ciprofloxacin, and 213 received fluocinolone otic solution. As the two trials were similar in design, pooled safety data are presented.

The median duration of exposure to Otovel was 7 days for all treatment groups.

There were no deaths in either trial. Three serious adverse events (SAEs) were reported including one case each of respiratory syncytial virus infection (Otovel arm), mastoiditis (ciprofloxacin arm), and right calf abscess (fluocinolone arm). None of the SAEs were considered to be related to study drug.

Fifteen patients had treatment emergent adverse events (TEAEs) leading to discontinuation from the study (3 in the Otovel arm, 5 in the ciprofloxacin arm, and 7 in the fluocinolone arm). In the Otovel arm, TEAEs leading to discontinuation from the study included worsening otitis media, acute otitis media, and fever. Thirty one patients had TEAEs resulting in discontinuation of study medication (5 in the Otovel arm, 8 in the ciprofloxacin arm, and 18 in the fluocinolone arm). Adverse events resulting in the discontinuation of study medications in the Otovel arm included worsening otitis media ($n = 2$), fever, upper respiratory infection and streptococcal throat infection.

TEAEs occurred in 96 (42.9%), 94 (42.7%), and 110 (51.6%) patients in the Otovel, ciprofloxacin, and fluocinolone arms, respectively. The incidence of TEAEs was similar between

treatment arms. The most frequent TEAEs in all treatment arms were pyrexia, otorrhea and ear pain. Selected adverse reactions reported by one or more patient in the Otovel arm are provided in Table 2.

**Table 2: Selected Adverse Reactions Occurring in ≥ 1 Patient in the Otovel Arm**

| | Number (%) of patients | | |
|---|---|---|---|
| **Adverse Reaction** | **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%) | 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%) |
| Auricular swelling | 1 (0.4%) | 1 (0.5%) | 0 (0.0%) |
| Balance disorder | 1 (0.4%) | 0 (0.0%) | 0 (0.0%) |

No safety laboratory assessments were performed. A behavioral audiometric assessment was performed at Visit 1 prior to administration of study treatment and at Visit 4 if the child was cooperative. Improvement was reported in 74%, 76.2%, and 72.2% of patients in the Otovel, ciprofloxacin, and fluocinolone arms, respectively, and worsening in 2%, 1.6%, and 3.7% of patients in the Otovel, ciprofloxacin, and fluocinolone arms, respectively.

(b)(4)

Drs. Ghosh and Kadoorie recommend approval of NDA 208251 for the treatment of AOMT in pediatric patients 6 months of age and older. Dr. Iarikov concurs with the assessment made by the review team and recommends approval of the NDA. I agree with their assessment.

## 8.0 Labeling

Labeling recommendations from Sevan Kolejian, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA), Adam George, PharmD, from the Office of Prescription Drug Promotion (OPDP), and Nyedra Booker, PharmD MPH, from the Division of Medical Policy Programs (DMPP) have been incorporated in labeling. The proposed proprietary name of Otovel was found acceptable.

## 9.0 Pediatrics

The Applicant's request for a partial waiver in children aged less than 6 months with AOMT was discussed by the Pediatric Review Committee (PeRC) on April 27, 2016, and found to be acceptable.

## 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. Three clinical sites with large subject enrollment were selected for inspection. A fourth site was not inspected as it had been recently inspected for a different study. No significant Good Clinical Practice (GCP) deficiencies were observed and a Form FDA 483 was not issued at any of the three sites. Dr. Lee notes that data from the three study sites appear reliable as reported in the NDA.

### Advisory Committee Meeting

This NDA was not discussed at an Advisory Committee meeting.

## 11.0 Risk Management

The Applicant has agreed to the following postmarketing commitment:

Submit tabulated results from the validation batches of the drug product (ciprofloxacin and fluocinolone acetonide otic solution, 0.3% / 0.025%) including actual yields for all unit operations and batch records along with results from all in-process tests.

Final Report Submission: November 2016

## 12.0 Regulatory Action

In summary, I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of Otovel (0.3 % ciprofloxacin and 0.025 % fluocinolone acetonide) Otic Solution for the treatment of acute otitis media in pediatric patients (aged 6 months and older) with tympanostomy tubes. Safety concerns are adequately addressed in labeling.

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

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/s/

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SUMATHI NAMBIAR
04/29/2016