CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208251Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dmitri Iarikov, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA #	208251, 505(b)(2)
Applicant	Laboratorios SALVAT, S.A.
Date of Submission	June 30, 2015
PDUFA Goal Date	April 30, 2016
Proprietary Name / Non-Proprietary Name	Otovel
Dosage form / Strength	Otic Solution / Each single-dose vial of ciprofloxacin 0.3 % and fluocinolone acetonide 0.025% otic solution contains 0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide in a deliverable volume of 0.25 mL.
Applicant Proposed Indication/Population	Acute otitis media with tympanostomy tubes (AOMT) / Patients aged 6 months and older
Recommendation on Regulatory Action	Approval

1. Introduction

This 505 (b)(2) NDA 208251 for Otovel (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025% otic solution) was submitted on June 30, 2015 to support the approval of Otovel for the treatment of acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. The applicant relies on the FDA finding of safety and efficacy for Cipro HC Otic (ciprofloxacin hydrochloride 0.2% and hydrocortisone 1%) otic suspension, NDA 20805, as reflected in the approved labeling. Cipro HC is approved for the treatment of acute otitis externa in pediatric and adult patients.

The safety and efficacy of Otovel for the treatment of AOMT is supported by two Phase 3 double-blind, randomized superiority trials where Otovel was compared with its individual components, i.e. ciprofloxacin 0.3% otic solution and fluocinolone acetonide 0.025% otic solution in the treatment of AOMT in pediatric patients. The results of these trials are the main subject of this review.

2. Background

Otovel is an otic solution consisting of ciprofloxacin hydrochloride 0.3% and fluocinolone acetonide 0.025%. Ciprofloxacin is a fluoroquinolone antimicrobial with activity against

several gram-positive and gram-negative organisms including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. Fluocinolone acetonide is a corticosteroid that is added to decrease local inflammation associated with bacterial infection.

Otovel is provided in single dose vials containing ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg in a deliverable volume of 0.25 mL. The contents of the single-dose vial are to be instilled into the affected ear twice daily for 7 days. This dosing regimen should be used for patients (b)(4).

The applicant relies on the FDA finding of safety and efficacy for Cipro HC Otic (ciprofloxacin hydrochloride 0.2% and hydrocortisone 1%) otic suspension, NDA 20805, as reflected in the approved labeling. Cipro HC is approved for the treatment of acute otitis externa in pediatric and adult patients. In particular, the applicant is relying on the prescribing information for Cipro HC on the genotoxic, carcinogenic and mutagenic potential of ciprofloxacin. The studies that support this information were conducted after systemic administration of ciprofloxacin, thus being applicable to any topical ciprofloxacin strength.

Other otic ciprofloxacin products include Ciprodex (ciprofloxacin hydrochloride 0.3% and dexamethasone 0.1%) otic solution, NDA 21537, approved for the treatment of acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes and for the treatment of acute otitis externa in pediatric and adult patients, and Cetraxal (ciprofloxacin hydrochloride 0.2%) otic solution, NDA 21918, approved for the treatment of acute otitis externa in pediatric and adult patients. Fluocinolone topical products include Derma-Smoothe/FS Topical Oil (fluocinolone acetonide 0.01%) which is approved for the treatment of atopic dermatitis, NDA 019452.

IND 107809 for ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution was submitted on December 20, 2010. NDA 208521 for ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution was submitted on June 30, 2015. The NDA included (b) (4) proposed indications, namely AOMT (b) (4) (b) (4)

The AOMT indication was supported by 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. The design of the trials was the subject of special protocol assessment and agreement was reached on May 2, 2011. NDA 208251/ Original-1 for the AOMT indication was found fileable.

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(b)(4)

3. CMC

The quality review was conducted by Haripada Sarker (drug substance), Milton Sloan (drug product), Dhana Kasi (process), Julie Nemecek (microbiology), Vidya Pai (facility), and Banu Zolnik (biopharmaceutics). All reviewers concluded that the NDA provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, ciprofloxacin and fluocinolone acetonide otic solution, and recommended approval of the NDA. The reader is referred to the integrated quality assessment review for detailed information about the review findings.

- *General product quality considerations*

The drug product is a sterile aqueous-based otic solution containing two drug substances, ciprofloxacin hydrochloride and fluocinolone acetonide. The product is packaged in a polyethylene 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. Each vial contains one dose of approximately 0.75 mg of ciprofloxacin and 0.0625 mg of fluocinolone acetonide. The excipients in the proposed formulation include polysorbate 80, glycerin, povidone K90F, and water for injection.

The proposed product shelf life of 24 months has been found acceptable. The product is to be stored at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). After opening the pouch the proposed storage time is 7 days. An individual vial is to be discarded after use.

- *Facilities review/inspection:*

All manufacturing and testing facilities for both drug substances and the drug product were found acceptable in support of this NDA.

- *Other notable issues*

The issues related to the low yield of the manufacturing process have been identified and will be further addressed via a post-marketing commitment. The product is manufactured and packaged (b) (4) manufacturing technology which (b) (4) The fill volume for manufactured batches is then tested and the batches with out of specification fill volume are rejected.

The identified issues are related to very low filling yield of exhibit batch 3C30 which was due to out of specification for fill volume. This was the only batch that was fully filled during the

Otovel clinical testing. Other exhibit batches were partially filled and the applicant did not provide the yield information for these bathes.

As a result, to demonstrate the robustness of the commercial manufacturing process the applicant will be asked to provide actual yields for all unit operations along with batch records and results from all in-process tests for the drug product validation batches via a post marketing commitment.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is Amy Ellis, Ph.D. The reviewer concludes that Otovel is reasonably safe for its intended use in humans and has no objection to approval of this NDA.

All of the nonclinical studies submitted in this NDA were reviewed previously under IND 107809. When administered intratympanically via a dosing catheter twice daily for 28 days to guinea pigs neither Otovel nor its vehicle induced cochlear hair cell loss. Otovel was, however, associated with mild to moderate hearing loss in female guinea pigs, as measured using Auditory Brainstem Response (ABR). The ABR data from guinea pigs treated with the vehicle for Otovel did not show treatment-related hearing loss.

The reviewer noted that it was unusual that only one gender appeared to be affected and commented that it is possible that the change was procedure-related. The reviewer also indicates that the guinea pig model is very sensitive for detecting potential ototoxicants and the dosing procedure used in the guinea pig studies maximizes middle and likely inner ear exposure to the test compounds. Additionally, the length of daily exposure to Otovel in the animal study (28 days) exceeded a 7-day duration of treatment proposed for clinical use.

Previous studies with 0.3% ciprofloxacin have shown that it was not toxic to cochlear hair cells when administered intratympanically to guinea pigs. Fluocinolone has not been previously studied for ototoxicity following intratympanic administration, but other corticosteroids, hydrocortisone and dexamethasone, did not appear to be ototoxic when given by this route.

Otovel was not a primary dermal irritant, based on a local lymph node assay conducted in mice or following dermal application to rabbits. No new genetic toxicology, long term carcinogenicity, and reproductive and developmental toxicity studies have been deemed necessary for Otovel because the product will be labeled for (b) (4) and the absorption of ciprofloxacin and fluocinolone following otic administration of Otovel at the recommended dosage is negligible. The reader is referred to the nonclinical pharmacology/toxicology review for more detail.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Dakshina Chilkuri, Ph.D. The clinical pharmacology review is focused on the evaluation of systemic concentrations of ciprofloxacin

and fluocinolone following their otic administration. The clinical pharmacology reviewer concludes that the systemic concentrations of both ciprofloxacin and fluocinolone in the majority of patients were below the limit of assay quantitation. The reviewer considers this information acceptable, and recommends approval of this NDA.

The review indicates that considering a low concentrations of ciprofloxacin (0.3%) in the proposed formulation and the maximum daily dosage of no more than 1 mL (in a case of bilateral AOMT), otic application is expected to result in systemic concentrations of ciprofloxacin that are much lower than those associated with oral or intravenous administration. Similarly, systemic absorption of topically applied fluocinolone is generally low.

Pharmacokinetic analysis of fluocinolone and ciprofloxacin in plasma samples was conducted in a subgroup of 14 patients from study CIFLOTIII/10IA04 and a subgroup of 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 with a limit of quantification for ciprofloxacin and/or fluocinolone in plasma samples of 1 ng/mL.

In both studies only 1 sample drawn from the patient with bilateral AOMT who consequently received a double dose of the drug showed a detectable concentration of ciprofloxacin in plasma (3 mcg/L) after 7 days of treatment. No detectable plasma concentrations of fluocinolone were observed. For comparison, according to the product information for ciprofloxacin hydrochloride, the maximum concentration in human serum after an intravenous infusion of 200 mg ciprofloxacin is approximately 2.1 mcg/mL, which is multi-fold higher than that observed after Otovel otic administration.

6. Clinical Microbiology

The clinical microbiology reviewer for this NDA is Kalavati Suvarna, Ph.D. The microbiology review is primarily focused on microbiological outcomes in the two Phase 3 trials submitted by the applicant to support the AOMT indication. The reviewer concludes that from a clinical microbiology standpoint the NDA can be approved.

In the Phase 3 trials Otovel (ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution) was compared with ciprofloxacin 0.3% and with fluocinolone acetonide 0.025% otic solutions. Study treatment was given for 7 days. The reader is referred to section 7 of this review for more detailed description of the design of these trials. Sustained microbiological cure was the principal secondary endpoint and was defined as eradication (no growth of any pathogen) or presumed eradication (no material to culture and the clinical response of clinical cure) at both the end of therapy (days 8 to 10) and test of cure (days 18 to 22) visits.

Sustained microbiological cure analyses were conducted in both microbiological intent-to-treat (MITT) and microbiological per-protocol (MPP) populations. The MITT population included all randomized patients whose Visit 1 microbiological culture of ear discharge yielded one or more pathogens. The MPP population included all randomized patients who did not have any

major protocol deviations and who had a baseline microbiological culture that yielded one or more pathogens and who had microbiological results from Visit 3 and/or Visit 4. Patients who had an infection that resolved to the extent that no culturable exudate was available were included in the MPP. Patients who were deemed a clinical failure at an earlier visit than the test of cure visit were also included.

One patient in study CIFLOTIII/101A02 was assigned to the fluocinolone group but received Otovel. This patient was included in the MITT population under the treatment assigned (fluocinolone) in the applicant's analysis but under the treatment actually received (Otovel) in the microbiology reviewer analysis.

The analysis of the principal secondary endpoint of sustained microbiological cure demonstrated that in both studies in the MITT and MPP populations the percentage of patients with sustained microbiological cure was greater in the Otovel group than in the ciprofloxacin and fluocinolone groups, **Table 1**. The difference reached statistical significance when Otovel was compared with fluocinolone but was not consistently significant when Otovel was compared with ciprofloxacin. Of note, the microbiology review does not include statistical analyses. Statistical parameters are provided based on the applicant analyses and included here to avoid repetition in subsequent sections of this review.

Table 1: Sustained Microbiological Cure the Phase 3 Studies of Otovel in Treatment of AOMT

	OTOVEL	**Ciprofloxacin**	**Fluocinolone acetonide**
Study CIFLOTIII/101A02 MITT population			
N	66	70	59
Yes, n (%)	48 (77.4%)	41 (65.1%)	22 (43.1%)
Total	62 (100%)	63 (100%)	51 (100%)
Missing	4	7	8
Pairwise comparison vs. Otovel P-value*		0.173	<0.001
MIPP population			
N	49	54	45
Yes, n (%)	42 (85.7%)	35 (70.0%)	17 (40.5%)
Total	49 (100%)	50 (100%)	42 (100%)
Missing	0	4	3
Pairwise comparison vs. Otovel P-value*		0.036	<0.001
Study CIFLOTIII/101A04 MITT population			
N	60	65	62
Yes, n (%)	47 (82.5%)	43 (70.5%)	18 (31.6%)
Missing	3	4	5
Total	57 (100%)	61 (100%)	57 (100%)
Pairwise comparison vs. Otovel P-value*		0.129	<0.001
MIPP population			

Table 1: Sustained Microbiological Cure the Phase 3 Studies of Otovel in Treatment of AOMT

	OTOVEL	Ciprofloxacin	Fluocinolone acetonide
N	40	56	46
Yes, n (%)	32 (82.1%)	37 (68.5%)	14 (31.8%)
Missing	1	2	2
Pairwise comparison vs. Otovel P-value*		0.149	<0.001

Source: Adapted from Table 9 and 14 in the FDA Microbiology Review, Table 11-9 in trials CIFLOTIII/101A02 and CIFLOTIII/101A04 study reports.
MITT: Microbiological intent-to-treat; MPP: microbiological per protocol.
* Cochran-Mantel-Haenszel test stratified on age (patients younger than 3 years old versus 3 years and older): pairwise comparisons without imputation of missing data.

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[redacted]

7. Clinical/Statistical - Efficacy

The clinical review was conducted by Mayurika Ghosh, M.D, and the statistical review was conducted by Christopher Kadoorie, Ph.D. The reviewers conclude that adequate evidence of efficacy of Otovel in the treatment of AOMT have been provided and are in agreement regarding interpretation of the trial results. The statistical reviewer primary and key secondary analyses were identical to those of the applicant.

The efficacy of ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution (hereafter Otovel) in the treatment of AOMT was supported by two randomized, double-blind, superiority Phase 3 trials comparing Otovel with ciprofloxacin 0.3% and fluocinolone acetonide 0.025% otic solution in the treatment of AOMT in pediatric patients aged 6 months to 12 years, trials CIFLOTIII/101A02 and CIFLOTIII/101A04 . Patients were randomized in a 1:1:1 ratio in each treatment group. Enrollment was stratified by age into 2 groups, i.e. subjects <3 and subjects ≥3 years old. Study medication was administered to the affected ear(s) twice daily for 7 days.

The trials consisted of 4 study visits:

- Visit 1 at Day 1: Screening, randomization/enrollment, baseline evaluation, ear exudate culture and start of treatment.
- Visit 2 at Day 3-5: Assessment of signs and symptoms of AOMT; decision to discontinue treatment and record as treatment failure.
- Visit 3 at Day 8-10: End of Treatment (EOT); ear exudate is collected if present.

- Visit 4 at Day 18-22: Post-treatment/Follow-up, Test of Cure (TOC); middle ear exudate is collected if present. Audiometric evaluation is performed in subjects who underwent that procedure at Visit 1.

The primary efficacy endpoint was the time to cessation of otorrhea. Otorrhea was defined as ending on the first day on which the otorrhea was absent and remained absent until the end of the study. Time to cessation of otorrhea was calculated in days as the date/time otorrhea ended minus the date/time of first dose of study medication. The primary analysis population was the clinical intent-to-treat (CITT) population that included all randomized patients.

The following subjects were censored at the maximum evaluation (i.e., Day 22):

- Patients who did not discontinue prematurely from the study and for whom the otorrhea still persisted at the end of the study.
- Patients who discontinued for any reason or who took rescue medication
- Patients lost to follow up, regardless of the status of otorrhea at the last observation.
- Randomized and non-dosed patients, regardless of their outcomes.

A total of 662 patients were randomized including 223 patients in the Otovel, 221 patients in the ciprofloxacin, and 218 patients in the fluocinolone group. Demographic and baseline characteristics were similar between the treatment groups. Mean age was 3.3 years and 58.2% of the patients were <3 years old. Slightly more than half the patients in each group were male (range: 57.8% to 61.1%). The majority of patients were White (77.2%); 13.3% of patients were Black or African American. The majority of patients (71.3%) were enrolled in the United-States.

In both trials the time to cessation of otorrhea in pediatric patients with AOMT was shorter in the Otovel than in the ciprofloxacin and fluocinolone groups demonstrating the contribution of both components of Otovel to its efficacy. Pairwise comparisons using the log-rank test, stratified by age (patients <3 years versus ≥3 years), revealed a statistically significant difference in time to cessation of otorrhea for Otovel compared with ciprofloxacin and fluocinolone. The results of the primary analyses are shown in **Table 2**.

Table 2: Time to Cessation of Otorrhea (CITT population)

Study CIFLOTIII/101A02	**OTOVEL (N=112)**	**Ciprofloxacin (N=109)**	**Fluocinolone acetonide (N=110)**
Number (%) of patients with cessation of otorrhea by Day 22	88 (78.6%)	73 (67.0%)	53 (48.2%)
Number (%) of censored patients	24 (21.4%)	36 (33.0%)	57 (51.8%)
Time to cessation (days)* Mean (SE) Median (95% CI)	6.9 (0.61) 3.8 (3.0, 4.4)	10.8 (0.78) 7.7 (4.8, 11.4)	12.6 (0.77) NE
Log-Rank test p-value vs OTOVEL**		<0.001	<0.001
Study CIFLOTIII/101A04	**OTOVEL (N=111)**	**Ciprofloxacin (N=112)**	**Fluocinolone acetonide**

			(N=108)
Number (%) of patients with cessation of otorrhea by Day 22	87 (78.4%)	77 (68.8%)	47 (43.5%)
Number (%) of censored patients	24 (21.6%)	35 (31.2%)	61 (56.5%)
Time to cessation (days)* Mean (SE) Median time to cessation (95%) (days)*	 7.6 (0.63) 4.9 (3.7, 5.5)	 10.5 (0.78) 6.8 (5.5, 7.7)	 13.7 (0.7) NE
Log-rank test p-value vs OTOVEL**		0.028	<0.001

Source: Adapted from Table 5,the FDA Statistical Review
CITT - Clinical Intent-to-Treat
NE: 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)

The results of the analyses of the principal secondary endpoint of sustained microbiological cure are discussed in section 6 of this review.

I agree with Dr. Ghosh and Dr. Kadoorie's conclusions that provided efficacy data are adequate to support approval of Otovel for the treatment of AOMT.

8. Safety

The clinical review was conducted by Dr. Mayurika Ghosh. She concludes that the safety profile of Otovel in the treatment of AOMT is acceptable and recommended approval of this NDA.

In the two Phase 3 clinical trials, 224 patients received Otovel, 220 patients received ciprofloxacin, and 213 patients received fluocinolone otic solution for the treatment of AOMT. The median duration of exposure to study medication was 7 days for all treatment groups. There were no deaths. Three serious treatment emergent adverse events were reported and none of them was considered to be related to study drug. These events included respiratory syncytial virus infection in the Otovel group, mastoiditis in the ciprofloxacin group, and right calf abscess in the fluocinolone group.

Fifteen patients had treatment emergent adverse events (TEAEs) leading to discontinuation from the study including 3 patients in the Otovel group, 5 patients in the ciprofloxacin group, and 7 patients in the fluocinolone group. In the Otovel group adverse events resulting in discontinuation from the study included worsening otitis media, acute otitis media, and fever.

Thirty one patients had TEAEs resulting in discontinuation of study medication, including 5 patients in the Otovel group, 8 patients in the ciprofloxacin group, and 18 patients in the fluocinolone group. Adverse events resulting in the discontinuation of study medications in the Otovel group included worsening otitis media (n=2), fever, upper respiratory infection and strep throat.

Any TEAEs occurred in 96 (42.9%), 94 (42.7%), and 110 (51.6%) patients in the Otovel, ciprofloxacin, and fluocinolone groups, respectively. There were no noticeable differences between the treatment groups in the incidence of TEAEs. The most frequent TEAE in all treatment groups was pyrexia followed by otorrhea and ear pain. **Table 3** presents selected adverse events observed in the AOMT trials.

Table 3: Selected Adverse Reactions That Occurred in 1 or More Patients in the Otovel Group (Safety Population)

Adverse Reactions*	Number (%) of patients		
	Otovel N=224	Ciprofloxacin N=220	Fluocinolone N=213
Otorrhea	12 (5.4%)	9 (4.1%)	12 (5.6%)
Ear pain	4 (1.8%)	4 (1.8%)	8 (3.8%)
Excessive granulation tissue	3 (1.3%)	0 (0.0%)	2 (0.9%)
Rash	2 (0.9%)	5 (2.3%)	4 (1.9%)
Ear infection	2 (0.9%)	3 (1.4%)	1 (0.5%)
Ear pruritus	2 (0.9%)	1 (0.5%)	1 (0.5%)
Auricular swelling	1 (0.4%)	1 (0.5%)	0 (0.0%)
Balance disorder	1 (0.4%)	0 (0.0%)	0 (0.0%)

Source: ISS/ISE ADaM – ADAE dataset, submission module 5.3.5.3
* The reactions that could be related to the study drug are selected

Safety laboratory assessments were not performed. Pharmacokinetic analysis of fluocinolone acetonide and ciprofloxacin in plasma samples was conducted in 30 patients. Only 1 sample showed a detectable concentration of ciprofloxacin (3 mcg/L) after 7 days of treatment. Of note, this plasma concentration of ciprofloxacin is considerably lower than that observed after systemic administration of ciprofloxacin. No detectable concentrations of fluocinolone acetonide were observed.

Behavioral audiometric assessment was performed at Visit 1 prior to administration of study treatment and at Visit 4 if the child was cooperative. Measured outcomes included no hearing loss, stable hearing loss, progressive conductive hearing loss, and progressive sensorineural hearing loss. The assessment showed improvement in 74%, 76.2%, and 72.2% of patients in the Otovel, ciprofloxacin, and fluocinolone groups, respectively and worsening in 2%, 1.6%, and 3.7% of patients in the Otovel, ciprofloxacin, and fluocinolone groups, respectively. Overall, there was no excess of sensorineural hearing loss in the ciprofloxacin-treated patients suggesting the absence of ciprofloxacin-related ototoxicity.

In conclusion, I agree with Dr. Ghosh conclusions that the results of the two Phase 3 clinical trials demonstrate an acceptable safety profile of Otovel in the treatment of AOMT.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this NDA.

10. Pediatrics

Otovel is proposed for the treatment of AOMT in pediatric patients aged 6 months and older. For children less than 6 months of age the applicant requested to waive clinical studies because myringotomy with tympanostomy tube placement is not usually performed in children of this age. The Division agreed to grant the waiver. The Pediatric Review Committee (PeRC) at its meeting on April 27, 2016 concurred with the waiver for clinical studies of Otovel in children less than 6 months of age.

11. Other Relevant Regulatory Issues

Three clinical sites with large subject enrollment were selected for good clinical practice inspection that was conducted by John Lee, MD, from the Office of Scientific Investigations. No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at the selected sites appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, case report forms (CRFs), and NDA data listings. The data from the three study sites appeared reliable as reported in the NDA.

12. Labeling

The proprietary name review was conducted by Sevan Kolejian, Pharm. D. from the Division of Medication Error Prevention and Analysis (DMEPA). The proposed proprietary name, Otovel, was considered acceptable. Patient labeling for Otovel was reviewed by Nyedra Booker, Pharm. D. from the Division of Medical Policy Programs (DMPP). The content of the draft package insert for Otovel was reviewed by Adam George, Pharm. D. from the Office of Prescription Drug Promotion (OPDP). In addition, the OPDP also reviewed the patient labeling and provided their comments in a collaborative consult response with the DMPP.

The recommendations from these reviews were incorporated in the labeling recommendations to the applicant. Work on the label was in progress at the time this review was written but there were no major unresolved labeling issues.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend approval of this 505 (b)(2) NDA 208251 for Otovel (ciprofloxacin 0.3 % and fluocinolone acetonide 0.025% otic solution) for the treatment of acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

The clinical trials of Otovel demonstrated that benefits of treatment outweigh the known risks. I agree with the primary reviewers that the applicant has provided sufficient evidence to support the safety and efficacy of Otovel in the treatment of AOMT.

Recommendations for Postmarketing Commitment

The applicant agreed to the following post-marketing 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: 11/2016

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/s/

DMITRI IARIKOV
04/29/2016