CLINICAL PHARMACOLOGY REVIEW

NDA	208251
Submission Date	June 30, 2015
Drug	OTOVEL (ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution)
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Philip M. Colangelo, PharmD, PhD
OCP Division	DCP4
OND Division	DAIP
Applicant	SALVAT Laboratories, SA
Submission Type	505(b)(1)
Formulation	Otic solution
Indication(s) and Dosage Regimen(s)	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) The contents of one single use vial (deliverable volume: 0.25 mL) should be instilled into the affected ear canal twice daily (approximately every 12 hours) for 7 days. This dosing regimen should be used for patients of all ages and for both indications.

1. EXECUTIVE SUMMARY

Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. The primary mode of action of the fluoroquinolones is inhibition of the bacterial DNA-gyrase and topoisomerase IV enzymes. Fluocinolone acetonide, like other topical corticosteroids, has anti-inflammatory, antipruritic, and vasoconstrictive properties and reduces the formation of granulation tissue. The addition of a corticosteroid to otic antibiotic preparations aids in the resolution of the inflammatory response accompanying bacterial infections. SALVAT Laboratories has developed OTOVEL, a sterile, preservative-free otic solution of the combination of ciprofloxacin 0.3% plus fluocinolone acetonide 0.025%, supplied in single-use vials. Each vial/application delivers 0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide.

NDA 208251 for OTOVEL was submitted for the treatment of acute otitis media in patients with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa,* (b) (4) . Most bacterial strains that cause (b) (4) AOMT are highly susceptible to ciprofloxacin.

Both drug substances currently are marketed for otic use in the US. Currently in the US, an otic formulation of ciprofloxacin 0.2% otic solution (CETRAXAL, SALVAT Laboratories, NDA 21-918, approved on May 1, 2009) is marketed for the treatment of AOE. Moreover, 2

otic formulations containing ciprofloxacin in combination with a corticosteroid have been approved and are marketed for acute otitis externa in both the pediatric and adult populations: CIPRO HC (ciprofloxacin 0.2% with hydrocortisone 1% suspension, Alcon, NDA 20-805, approved February 10, 1998), and CIPRODEX (ciprofloxacin 0.3% with dexamethasone 0.1% sterile otic suspension, Alcon NDA 21-537 approved July 18, 2003). CIPRODEX is also approved for the topical treatment of AOMT in children aged 6 months and older.

The combination of ciprofloxacin plus fluocinolone acetonide otic solution is currently approved in over 40 countries outside the US, including some major EU countries, and is indicated for the local treatment of AOE of bacterial origin. The applicant's clinical development program for this combination (b) (4) in AOMT includes two twin phase III, multicenter, randomized, double-blind clinical trials (CIFLOTIII/10IA02 and CIFLOTIII/10IA04) to assess the efficacy and safety in the treatment of AOMT in pediatric patients aged 6 months and older.

The NDA 208521 submitted by SALVAT Laboratories (b) (4) :

- NDA 208251/Original-1 – Acute Otitis Media in Patients with Tympanostomy Tubes (AOMT)

(b) (4)

(b) (4)

(b) (4)

The subject of the clinical pharmacology review of this NDA was to evaluate the systemic concentrations of ciprofloxacin and flucinolone when administered as an otic solution in both clinical studies (mentioned above). For a discussion of the clinical efficacy results, please refer to the review by the clinical reviewer, Dr. Mayurika Ghosh.

Given the low concentration of ciprofloxacin in the formulation (0.3%), and the maximum daily dosage volume to be administered (b) (4) mL per day), topical application in the ear is expected to result in systemic concentrations of ciprofloxacin that are much lower than those following oral or intravenous administration. Likewise, the systemic absorption of

fluocinolone acetonide after topical administration is generally low, and varies according to the application site. However, no safety pharmacology studies have been conducted to support the development of ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% by otic administration. Nonetheless, systemic concentrations of either active ingredient after otic administration of the recommended dose of OTOVEL would be expected to be below those following systemic administration of either drug.

Pharmacokinetic analysis of fluocinolone acetonide and ciprofloxacin in plasma samples was conducted in a subgroup of patients in the two above-mentioned studies. In the applicant's AOMT clinical trials, a subgroup of 14 patients from study CIFLOTIII/10IA04 and a subgroup of 16 patients from study CIFLOTIII/10IA02 participated in the PK portion of the two studies. The dosage regimen used in both studies was the following: the contents of one single use vial (deliverable volume: 0.25 mL) were instilled into the affected ear canal twice daily (approximately every 12 hours) for 7 days. This dosing regimen was used for patients of all ages and for both indications. 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 in plasma samples of 1 ng/mL.

In Study CIFLOTIII/10IA02, only 1 sample, drawn from the patient who received a double dose of the drug due to bilateral AOMT, showed a detectable concentration of ciprofloxacin in plasma (3 µg/L) after 7 days of treatment, and no detectable concentrations of fluocinolone acetonide in plasma were observed. The patient did not present any treatment-emergent adverse events (TEAE).

In Study CIFLOTIII/10IA04, PK analysis of fluocinolone acetonide and ciprofloxacin in plasma samples was conducted for a subgroup of 14 patients. No detectable concentrations of fluocinolone acetonide in plasma were observed after 7 days of treatment, and no ciprofloxacin results were reported.

(b) (4)

If ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution is dosed in accordance to the proposed dosage regimen of 0.25 mL BID for (b) (4) AOMT (b) (4) the total amount of drugs administered daily would be 1.5 mg of ciprofloxacin and 0.125 mg of fluocinolone acetonide. This quantity will be double in case of bilateral disease (recognizing that (b) (4) approximately 20% had bilateral AOMT). According to the product information for ciprofloxacin hydrochloride, the maximum concentration (C_{max}) in human serum after an intravenous infusion of 200 mg ciprofloxacin is approximately 2.1 µg/mL. Thus, if 100% of a 3-mg dose were absorbed systemically, the expected C_{max} would be 31.5 ng/mL, which is approximately 67-fold less than 2.1 µg/mL. However, it is likely that only a small fraction of the administered dose is systemically absorbed, especially if the tympanic membrane is intact.

2. RECOMMENDATIONS

The Clinical Pharmacology information submitted by the applicant in NDA 208251, Original 1 for AOMT (b) (4) for OTOVEL is limited and the systemic concentrations of both ciprofloxacin and fluocinolone acetonide in the majority of patients were below the limit of assay quantitation. Nonetheless, the Clinical Pharmacology team deems this information acceptable, and recommends approval of this NDA, pending agreement on the recommended edits to the applicant proposed labeling.

3. PROPOSED LABELING

The relevant Clinical Pharmacology sections as proposed by the applicant in the label are given below. The following changes are proposed by the Clinical Pharmacology reviewer (deletions noted as strikethrough; additions by yellow highlights and underlined):

(b) (4)

Section 12.3. Pharmacokinetics

In two studies (b) (4) in children with (b) (4) (AOMT) aged ≥6 months to 12 years, blood samples were taken in subgroups of 16 and 14 patients, (b) (4) at Visit 1 (prior to the first dose) and Visit 3 (within 1 and 2 hours after the last dose) to determine the plasma concentrations of ciprofloxacin and/or fluocinolone acetonide following administration of OTOVEL otic solution at the recommended dosage regimen of 0.25 mL BID. Pharmacokinetic (PK) analysis resulted in only 1 sample showing a detectable concentration of ciprofloxacin in plasma of 3.0 µg/L after 7 days of treatment, and no detectable plasma concentrations of fluocinolone acetonide were observed. However, the sample with detectable ciprofloxacin concentrations was from a patient who had bilateral AOMT (protocol deviation because all patients participating in the PK study were to have unilateral otorrhea) and who received treatment in both ears with ciprofloxacin 0.3% otic solution, the active comparator.

(b) (4)

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/s/

DAKSHINA M CHILUKURI
03/11/2016

PHILIP M COLANGELO
03/14/2016