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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208251
Supporting document/s:	SD-1
Applicant's letter date:	6/30/15
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Product:	(b)(4) (Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution)
Indication:	Acute otitis media in pediatric patients aged 6 months and older with tympanostomy tubes
Applicant:	Laboratorios Salvat (Barcelona, Spain)- U.S. representative is Premier Research (Philadelphia, PA)
Review Division:	Anti-Infective Products
Reviewer:	Amy L. Ellis, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Sumathi Nambiar, M.D., MPH
Project Manager:	Carmen DeBellas, Pharm.D.

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1 Executive Summary

1.1 Introduction

Salvat markets (outside of the U.S.) a product containing ciprofloxacin and fluocinolone acetonide (b) (4). They also market (in both the U.S. and abroad) a product with ciprofloxacin alone (Cetraxal) for treating acute otitis media in patients with tympanostomy tubes (AOMT). There are other products marketed in the U.S. for treatment of AOMT that contain ciprofloxacin at a similar concentration. Fluocinolone has not been previously studied for otic indications, but it has been used in topical dermal products and another corticosteroid, dexamethasone, is a component of an otic suspension used for treating AOMT.

1.2 Brief Discussion of Nonclinical Findings

Cytocochleogram analysis showed that neither (b)(4) nor its vehicle induced cochlear hair cell loss in guinea pigs dosed intratympanically with these solutions twice daily for 28 days. However, (b)(4) was associated with mild to moderate hearing loss in female guinea pigs, as measured using Auditory Brainstem Response (ABR). It was unusual that only one gender appeared to be affected and it is possible that the change was procedure-related. The ABR data from guinea pigs treated with the vehicle for (b)(4) did not show treatment-related hearing loss. 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, hydrocortisone and dexamethasone, did not appear to be ototoxic when given by this route.

(b)(4) was not a primary dermal irritant, based on a local lymph node assay conducted in mice or following dermal application to rabbits.

The amount of (b)(4) that reaches the middle ear space during clinical use by patients with tympanostomy tubes is not likely to be as great as that which was present in the guinea pigs that were the subjects in the ototoxicity study. 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, (b)(4) is considered to be reasonably safe for its intended use in humans.

1.3 Recommendations

1.3.1 Approvability

No objection to approval of this drug product.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The Established Pharmacologic Class listed for ciprofloxacin is “quinolone antimicrobial”, but there has been discussion that it may be changed to “fluoroquinolone antimicrobial”. The EPC for fluocinolone is “corticosteroid”.

Work on the label is in progress. Section 8.1 will follow the PLLR. No studies with (b)(4) have been performed in either pregnant women or animals. Thus, as permitted under section 505(b)(2), language regarding reproductive and developmental toxicity potential for (b)(4) can be drawn from labels of approved products containing the same active ingredients. Systemic ciprofloxacin exposure has been demonstrated to be minimal following otic application to patients with AOMT (including (b)(4) and other similar products). There are clear no-effect levels in animal reproduction and developmental toxicity studies with ciprofloxacin. Fluocinolone has not undergone reproduction and developmental toxicity testing. There is class labeling for corticosteroids regarding teratogenicity that has been used in other products containing fluocinolone. However, because fluocinolone exposure is very low following otic application of (b)(4) to patients with AOMT, there is concern on the review team that the class language may not be relevant for this product. (b)(4) is applied to a smaller body surface area than topical creams containing corticosteroids. The Clinical members of the review team will look for information on the use of fluocinolone or related corticosteroids in patients that may help them to write a risk statement that is more relevant for (b)(4)

The sponsor included mutagenicity and fertility data in section 8.1. These will be moved to Section 13. This section will also contain carcinogenicity information taken from approved labels of products containing ciprofloxacin or fluocinolone.

2 Drug Information

2.1 Drug

CAS Registry Numbers:
Ciprofloxacin: 86393-32-0
Fluocinolone: 67-73-2

Generic Name: Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution

The trade name (b) (4) was deemed unacceptable by DMEPA because its spelling and pronunciation are similar to the currently marketed product (b) (4). The sponsor has submitted a new trade name, OTOVEL.

During the initial testing phase with this product, it was called (b) (4) This name was used in some of the nonclinical study reports.

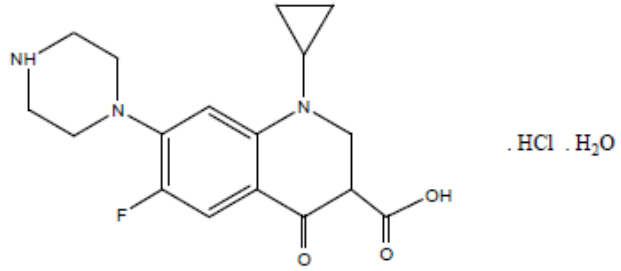
Code Names:
Ciprofloxacin: 1058
Fluocinolone: 2151NM1

Chemical Names:
Ciprofloxacin: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate
Fluocinolone: 6α, 9 α -Difluoro-11β,16α,17,21-tetrahydroxypregna- 1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone.

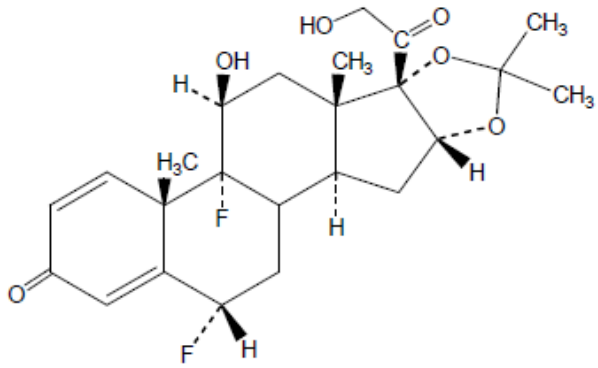
Molecular Formula/Molecular Weight:
Ciprofloxacin: $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$ / 385.8
Fluocinolone: $C_{24}H_{30}F_2O_6$ / 452.49

Structures:

Ciprofloxacin:



Fluocinolone:



Pharmacologic Classes: Fluoroquinolone antimicrobial and corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

The IND for Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution is 107809.

There are several approved NDAs for products containing ciprofloxacin (numerous routes, both systemic and topical- including otic) and fluocinolone (topical). However, the sponsor does not have right of reference for any of these.

Also relevant is the sponsor's approved NDA 21-918 0.2% ciprofloxacin otic solution for the treatment of acute otitis externa.

2.3 Drug Formulation

From the submission:

Table 1: Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution Composition (per vial)

Ingredient	Amount (%) per unit dose	Functional category
Ciprofloxacin Hydrochloride USP	(b) (4)	Active ingredient
Fluocinolone Acetonide USP		Active ingredient
Polysorbate 80 NF		(b) (4)
Glycerin USP		
Povidone K90F USP		
Water for injection USP		

[1]Equivalent to 750 µg (0.300%) Ciprofloxacin base

This table from the submission shows the batches of product that were used for nonclinical testing:

Test Article: Ciprofloxacin/Fluocinolone acetonide						
Drug product	**DP Lot No.**	**Assay[a] (mg/mL)**	**Total Impurities[a] (%)**	**Report Number**	**Study Type**	**Route of Administration**
(b) (4)	G124/066P	NA	(b) (4)	(SALVAT) CD01/7657T	Repeat dose toxicity - otic	Otic
	G124/066P	NA		(SALVAT) CD01/7588T	Local tolerance	Dermal
Cetraxal Otico[c]	G00388	NA		(SALVAT) Rabbit 1993	Local tolerance	Dermal
(b) (4)	DF256-080	NA		(SALVAT) B-01068	Local tolerance	Dermal
	DF256-086	NA		(SALVAT) 3191/0001	LLNA	Dermal
	DF256-082	NA		(SALVAT) 1856-001	Repeat dose toxicity	Intratympanic

[a] Assay and total impurity data are obtained from the Certificates of Analysis and reflect the current method at the time of release of the batch
[b] 0.3% Ciprofloxacin + 0.025% Fluocinolone acetonide
[c] 0.3% Ciprofloxacin
(b) (4)
Abbreviations: DP = Drug Product; LLNA= Local lymph node assay; NA = Not available

2.4 Comments on Novel Excipients

Although the inactive ingredients polysorbate 80, glycerin, and povidone K90 have been used in products applied to the external ear canal when the tympanic membrane (TM) is intact, they do not appear to have been previously used in products intended for application to ears with a non-intact TM (e.g., TM with tympanostomy tubes). The guinea pig otic repeat dose toxicity study (1856-001) was adequate to demonstrate the safety of these ingredients for use when the TM is not intact.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

The product is indicated for treatment of acute otitis media in pediatric patients (≥ 6 months of age) with tympanostomy tubes (AOMT).

The contents of one (b) (4) vial (0.25 ml, containing 0.75 mg of ciprofloxacin and 0.0625 mg of fluocinolone acetonide) will be instilled into the affected ear canal twice daily (about 12 hours apart) for 7 days.

2.7 Regulatory Background

Development of this product occurred under PIND/IND 107809. Initially, this NDA was (b)(4)

3 Studies Submitted

3.1 Studies Reviewed

All of the nonclinical studies submitted in this NDA were reviewed previously under IND 107809 (see below)

3.2 Studies Not Reviewed

Primary Skin Tolerance of the Medicine CETRAXAL OTICO in Rabbits (dated April 1993, not GLP and no Study No. provided)- this study was not conducted with the product that is the subject of this NDA, but with another product belonging to the sponsor which contains ciprofloxacin only

3.3 Previous Reviews Referenced

The following studies were reviewed under IND 107809 SD-6 (original IND submission):

Otic Tolerance From Continuous Administration Over Four Weeks in the Guinea Pig. Topical Route Test Substances: G124/066P and G124/073 (Protocol No. CD01/7657T)

Primary Dermal Irritation in the Rabbit: Test Substance G124/066P (Active) (Report No. CD01/7588T-1)

Evaluation of the Acute Dermal Irritant and/or Corrosive Effect of (b)(4) After a Single Dose Administration to Female New Zealand White Rabbits (Report No. B-01068)

(b)(4) Local Lymph Node Assay in the Mouse (Project No. 3191/0001)

This draft report of this study was reviewed in the original IND 107809 submission, and the final report was reviewed in IND 107809 SD-10:

A 28-Day Subacute Ototoxicity Study of (b)(4) Otic Solution in Guinea Pigs-Unaudited Data with Executive Summary (Study No. 1856-001)

4 Pharmacology

4.1 Primary Pharmacology

Ciprofloxacin interferes with the enzyme DNA gyrase and inhibits DNA synthesis in susceptible bacteria. Fluocinolone inhibits the inflammatory process.

4.3 Safety Pharmacology

Not necessary/relevant for this product.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetic or toxicokinetic studies were performed with (b)(4) in animals and none were necessary. Each dose contains relatively small amounts of ciprofloxacin and fluocinolone. The distribution, metabolism, and excretion of both drugs have been studied previously in animals and humans to support their uses as an antimicrobial (systemic, ophthalmic, and otic) and a corticosteroid anti-inflammatory (dermal, ophthalmic).

From the Ciprofloxacin Tablet label:

After oral administration, ciprofloxacin is widely distributed throughout the body.

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

From the label for Fluocinolone Acetonide Topical Solution:

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

6 General Toxicology

Ototopical application of (b)(4) or its vehicle to guinea pigs with intact tympanic membranes was tolerated for a period of 4 weeks without any significant adverse effects. The only otic change that may have been compound-related was minor irritation in the outer ear canal of a single animal treated with (b)(4)

Cytocochleogram analysis showed that neither (b)(4) nor its vehicle induced cochlear hair cell loss in Hartley guinea pigs dosed intratympanically (via transbullar catheters) with these solutions twice daily for 28 days. The Auditory Brainstem Response data from guinea pigs treated with the vehicle for (b)(4) did not show treatment-related hearing loss. ABR results from animals treated with (b)(4) showed mild to moderate hearing losses in most of the females, but not the males. This did not correlate with hair cell loss and may have been procedure-related. Neomycin, the positive control, caused moderate to severe hearing loss and hair cell loss in the animals exposed to it.

7 Genetic Toxicology

No new genetic toxicology studies were submitted for either ciprofloxacin or fluocinolone.

According to the labels of currently marketed products containing ciprofloxacin or fluocinolone:

In vitro, ciprofloxacin was negative in the Ames *Salmonella* reversion assay, an *E. coli* DNA repair assay, the Chinese Hamster V_{79} Cell HGPRT test, the Syrian Hamster Embryo (SHE) Cell transformation assay, *Saccharomyces cerevisiae* point mutation assay, and *Saccharomyces cerevisiae* mitotic crossover and gene conversion assay. It was, however, positive in the Mouse Lymphoma Cell forward mutation assay and the rat hepatocyte DNA repair assay. *In vivo*, ciprofloxacin was negative in the rat hepatocyte DNA repair assay, a mouse micronucleus test, and a dominant lethal test also conducted in mice.

Studies have not been performed to evaluate the mutagenic potential of fluocinolone acetonide. Some corticosteroids have been found to be genotoxic.

8 Carcinogenicity

No long term studies of (b)(4) are needed to evaluate its carcinogenic potential. The product will be labeled for (b) (4)

According to the labels of currently marketed products containing ciprofloxacin or fluocinolone:

Two year bioassays conducted in rodents using daily oral doses of ciprofloxacin up to 750 mg/kg (mice) and 250 mg/kg (rats) revealed no evidence of carcinogenesis.

Carcinogenicity studies have not been conducted with fluocinolone.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity studies have not been performed with (b)(4) and none are needed.

According to the labels of currently marketed products containing ciprofloxacin or fluocinolone:

Oral doses of ciprofloxacin up to 100 mg/kg/day were not associated with impairment of fertility in rats. Ciprofloxacin was not teratogenic or embryotoxic to rats or mice after administration of maternal oral doses up to 100 mg/kg or IV doses up to 30 mg/kg. In rabbits, oral doses >30 mg/kg were associated with gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but not

teratogenicity. Maternal toxicity was not observed in rabbits given IV doses of ciprofloxacin <20 mg/kg and neither embryotoxicity or teratogenicity was observed in the offspring. These sort of findings in rabbits are common to many antimicrobial drug products.

No adequate animal fertility, reproductive, or developmental toxicology studies have been conducted with fluocinolone. However, corticosteroids are generally teratogenic in laboratory animals when they are administered systemically at relatively low dose levels and the more potent of these compounds are animal teratogens when dermal routes of administration are used.

10 Special Toxicology Studies

When applied for up to 4 hours under semi-occlusive patches, neither (b)(4) nor its vehicle was an acute irritant to New Zealand White rabbit skin. For (b)(4) only very mild (score of 1 on a scale of 0-4) erythema and edema were observed after a 4 hour dermal exposure under a semi-occlusive patch. The very mild erythema persisted for 48 hours, but was not observed after 72 hours. The very mild edema was not observed by 24 hours after exposure.

A local lymph node assay conducted in female CBA/Ca mice with (b)(4) and its vehicle was negative.

11 Integrated Summary and Safety Evaluation

Neither (b)(4) nor its vehicle was an acute dermal irritant in rabbits. These articles were not skin sensitizers when applied to the ears of mice in a local lymph node assay.

Ototopical application of (b)(4) or its vehicle to guinea pigs with intact tympanic membranes was tolerated for a period of 4 weeks without any significant adverse effects. The only otic change that may have been compound-related was minor irritation in the outer ear canal of a single animal treated with (b)(4).

A 28-day study in guinea pigs where (b)(4) vehicle, normal saline (negative control), or neomycin (positive control) were administered intratympanically via a dosing catheter through the bulla showed that the vehicle does not appear to be ototoxic. However, (b)(4) was associated with mild to moderate hearing losses in most of the females, but not the males. Hearing function was tested using ABR (auditory brainstem response). It is unusual to see different results in male and female animals from the same treatment group in an ototoxicity study with test articles administered directly into the middle ear (thus, no differences in exposure based on kinetics). Moderate to severe (mostly the latter) hearing losses were observed in all animals that were treated with neomycin, the positive control. The ABR changes observed in the females treated with (b)(4) were not comparable to those observed with neomycin. Cytocochleogram analysis showed that neither (b)(4) nor its vehicle induced hair cell loss in the guinea pigs, suggesting that the moderate hearing losses detected in females from the (b)(4)

group may be procedure-related as opposed to an irreversible loss due to the death of cochlear hair cells.

Previous guinea pig ototoxicity studies with ciprofloxacin administered into the middle ear have shown this compound to have a low potential for ototoxicity, although, when treated with higher concentrations of ciprofloxacin (e.g., 1% as opposed to 0.3-0.5%) some individual animals have had moderate hearing loss accompanied by middle ear inflammation (which can cause conductive hearing loss likely to be reversible when the inflammation subsides) and occasionally some modest outer hair cell loss (associated with sensorineural hearing loss at high frequencies and unlikely to be reversible). Guinea pig ototoxicity studies with other steroids such as hydrocortisone and dexamethasone suggested that these steroids are unlikely to be ototoxicants when used to treat patients with tympanostomy tubes. Likewise, fluocinolone is not expected to be ototoxic.

The guinea pig model is very sensitive for detecting potential ototoxicants. The amount of test article that is administered directly into the middle ears of these animals twice daily is greater than the amount likely to reach the middle ears of patients with tympanostomy tubes. Additionally, 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 the former to compounds that are administered intratympanically.

Thus, (b)(4) is considered unlikely to be ototoxic to humans when used as proposed to treat AOMT.

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/s/

AMY L ELLIS
04/01/2016

WENDELYN J SCHMIDT
04/01/2016
I concur with Dr. Ellis's interpretation of the data as well as her assessment of the adequacy of the package.