Samanta, Susmita

From:	Duvall Miller, Beth A
Sent:	Tuesday, April 14, 2009 8:10 AM
To:	Samanta, Susmita
Cc:	Quaintance, Kim M
Subject:	RE: NDA 21-918 - cleared for action

Susmita,

We discussed your application at yesterday's clearance meeting with OCC/ORP. It is cleared for action from a b(2) perspective.

Please make sure that the bridging rationale is documented in someone's review.

Thanks,

Beth

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Samanta, Susmita
Sent: Wednesday, April 08, 2009 3:59 PM
To: Duvall Miller, Beth A
Subject: RE: NDA 21-918 - b(2) clearance questions

Hi Beth,

Thank you for reviewing my application, I know it was tricky. Here are my responses to the best of my knowledge. I wanted to pass this by the MO, but he is out.

From:	Duvall Miller, Beth A
Sent:	Tuesday, April 07, 2009 12:19 PM
To:	Samanta, Susmita
Cc:	Quaintance, Kim M
Subject:	NDA 21-918 - b(2) clearance questions

Hi Susmita,

I've completed my review of this application which was tricky given that I was trying to make sense of an email string from 2006 (attached) that pre-dates my involvement with b(2) s. So forgive me if some of my questions were previously asked/answered – the attached email was all I had to go by. That said, I have a few questions for you in preparation for Monday's discussion of your application:

- It appears the applicant amended (in August 2005) their original application to cite reliance on the other two Cipro products, NDAs 19-537 and 21-537 because

these applications were specifically named in the clin pharm lit studies necessary for approval of this application. Is that correct?

Yes, it is correct

- How did the applicant bridge their proposed product to the products they are relying on? In your filing review, you indicated "n/a" in response to the question whether BA/BE studies were conducted.

  Compared to the cipro products this application relies on, the proposed product contains a lower concentration of ciprofloxacin delivered in higher volume of solution than the approved products. Therefore the applicant performed a single clinical trial to provide evidence of the safety and effectiveness of Cetraxal in the treatment of acute otitis externa.

- Kim's hanging question at the top of the attached email string asked whether or not there were other statements added to the Cipro label (19-537/S-049) other than the pediatric indication (UTI and pyelonephritis). (Sorry if you had previously answered this question). I was able to pull the S-049 AP letter from DFS (attached), but unfortunately the attached labeling is not marked up. If you have the current version of the Cetraxal label to send us, that would be very helpful, particularly an annotated version.

  I am attaching the current proposed label for Cetraxal. This drug is a an otic product with very little systemic absorption with no added safety issue.

<< File: 21918.label.213.doc >>

Please let me know if you have any other questions.

Thank you

Suamita

<< File: N21918_email string.pdf >> << File: N21918_Cipro S049 AP ltr.pdf >>

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Samanta, Suamita
Sent: Monday, February 02, 2009 9:46 AM
To: Duvall Miller, Beth A
Subject: RE: NDA 21-918

h,

Good morning. We would probably take action on this my mid April.

Thank you

Susmita

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-918

Laboratorios SALVAT, S.A.
Attention: John F. Worzalla
Anson Group, Suite 150
11460 N. Meridian St.
Carmel, IN 46032

Dear Mr. Worzalla:

We acknowledge receipt on November 3, 2008, of your October 31, 2008 resubmission to your new drug application for CETRAXAL® (ciprofloxacin otic solution), 0.2%.

We consider this a complete, class 2 response to our January 29, 2008 action letter. Therefore, the user fee goal date is May 3, 2009.

If you have any questions, call Susmita Samanta, MD, Regulatory Project Manager, at 301-796-0803.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Frances LeSane
12/11/2008 10:28:49 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 25, 2006

TO: Susmita Samanta, Regulatory Project Manager, HFD-520
Frances LeSane, Regulatory Project Manager, HFD-520
John Alexander, M.D., Clinical Review Team-Leader, HFD-520
Nasim Moledina, M.D., Clinical Reviewer, HFD-520
Janice Soreth, M.D., Director, HFD-520
Division of Anti-Infective Drug Products, HFD-520

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II/HFD-47
Division of Scientific Investigations (DSI)

FROM: Mathew T. Thomas, M.D.
Reviewer
Good Clinical Practice Branch II

SUBJECT: Summary of Clinical Investigator Site Inspection

NDA: #21-918
APPLICANT: Laboratorios SALVAT, S.A.
DRUG: Ciprofloxacin otic solution 0.2%

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of Acute Otitis Externa in Adult and Pediatric Patients 1 year and older.

SUBMISSION DATE: June 9, 2005
CONSULTATION REQUEST DATE: August 30, 2005
DSI ACTION GOAL DATE: February 15, 2006
PDUFA DATE: April 9, 2006

I. BACKGROUND:

The Review Division (HFD-520) requested a routine data audit inspection of two study sites that conducted study Protocol #CIPROT III IA 02 and from which data was submitted in support of NDA#21-918.

In this study ciprofloxacin otic solution 0.2% was compared to reference treatment, neomycin and polymxin B sulfates and hydrocortisone (PNH) otic solution, in the treatment of acute diffuse otitis externa (OE) in children, adolescents and adults.

Primary efficacy endpoint was the proportion of clinical per-protocol patients with clinical cure (Pain, edma, and otorrhea resolved at Visit 4 (15 to 17 days post-treatment follow-up).

Adverse events were any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the product.

II. RESULTS OF CLINICAL INVESTIGATOR DATA AUDIT (by site):

Name	City, State	Country	Protocol	Insp. Date	EIR Received	Classification
Gary Goldstein	Palm Harbor, FL	USA	CIPROT III	12/5 to 8/2005	12/30/05	NAI
John Champlin	Carmichael, CA	USA	CIPROT III	11/15 to 18/2005	Pending	VAI

EIR Pending = EIR not received from the FDA Field District Office.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Gary Goldstein, M.D.
3890 Tampa Road, Suite #102
Palm Harbor, FL 34684

1. What was inspected?

The FDA field investigator reviewed the case histories of 20 of the 28 subjects that were screened for the study. Source document review included informed consent forms, medical charts, progress notes, laboratory test results, and physical examination records.

2. Limitations of the Inspection: None.

3. General observations/commentary:

Twenty-eight subjects were screened at this study-site; 26 subjects were randomized; 25 subjects completed the study. The records of about 20 subjects' were reviewed and no significant violation was observed.

One subject (subject #28) was discontinued from treatment and the blind was broken. The exact cause for discontinuation remains unknown but the following were cited as the possible reasons; possible allergic reaction to test article, a resistant organism, or worsening of cellulitis; in that the infection was going deeper and involving more tissue. It appears that this data was reported to the reviewing division.

The study appears to have been conducted adequately, and the data generated by this study site and submitted in support of the NDA appears acceptable.

B. John Champlin, M.D.
6651 Madison Avenue
Carmichael, CA 95608

1. What was inspected?

The FDA field investigator reviewed the case histories of 16 of the 32 subjects that were screened for the study. Record review included a review of source documents, data listings and study data, IRB and sponsor correspondence, drug accountability, blinding and randomization procedures, and protocol deviations. All informed consent forms were reviewed.

2. Limitations of the Inspection: None. DSI has not received the EIR for this inspection. The information discussed below is gathered from the FDA Form 483, Inspectional Observations, which was issued to the clinical investigator (CI) at the conclusion of the inspection and additional communications that the FDA Field Investigator sent to DSI. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. General observations/commentary:

Thirty-two subjects were enrolled at this study site. Reportedly, 3 of the 32 subjects did not complete the study. The subjects who did not complete the study were #003, #006 and #023.

Based on a review of 16 of the 32 subjects' records (Subject #s 001, 002, 003, 004, 005, 008, 013, 019, 022, 023, 024, 025, 026, 030, 031, and 032) the FDA Field investigator reported the following observations:

a. Protocol deviations that were not reported by the clinical investigator to the sponsor:
   i. Subject #001 was enrolled on 6/21/04 but took Advil on 6/20-22/04. (A violation of protocol sections 6.7.1. and 5.2.2.)
   ii. Subject #005 missed 3 consecutive doses (afternoon and evening of July 1, 2004 and morning of July 2). The clinical research coordinator (CRC) instructed the subject to make up 3 doses on day 8, July 6, 2004. (See protocol section 6.2, second paragraph).
   iii. Subject #022 swam between Visit 3 and Visit 4. (See protocol section 4.1, second paragraph).
   iv. Subject #024 had a discharge from the ear at Visit 3 (9/8/04) but the CRC forgot to collect lab sample (See protocol sections 7.1.2, 8.1, and 8.2.3).
   v. Subject #026 was taking Sudafed 3x/day for ear ache and pressure up to time of study entry on 9/10/04. (A violation of protocol exclusion criteria – section 5.2.2.)

b. Three (3) adverse events (AEs) were not reported:
   i Subject #022, experienced worsening of OE and reported to sub-investigator (sub-I) by phone on or about 8/22/04. Sub-I examined and treated the subject at Visit 3 on 8/23/04 and started subject on Keflex 250mg PO TID.
   ii. Subject #024, experienced increased pain and discharge in the affected right ear on 9/1/04 (between Visit 1 & Visit 2). Worsening of symptoms was not reported as an AE.
   iii. Subject #030 reported experiences of increased pain and discharge in the affected ear at Visit 4 (10/11/04).

The review division medical officer should review the above mentioned unreported protocol deviations and adverse events to determine if they significantly impact the study data submitted by the sponsor in support of NDA 21-918.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The Review Division (HFD-520) selected two sites for routine data audit inspection of the study Protocol CIPROT III/03 IA 02 submitted in support of NDA#21-918.

Based on the results of the inspections it appears that the data submitted in support of this application from Dr. Goldstein's study site is acceptable.

The observations noted above for the data from Dr. Champlin's study site are based on the Form FDA 483, and communications from field investigator. The data from Dr. Champlin's study site may be deemed acceptable if the review division medical officer determines that the above mentioned issues are not significant enough to adversely impact the overall study data. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Signature
Mathew T. Thomas, MD
Division of Scientific Investigations

CONCURRENCE: Supervisory comments.

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II/HFD-47
Division of Scientific Investigations

DISTRIBUTION:
Division File: NDA #21-918
HFD-45/Division File
HFD-47/Program Management Staff (electronic copy)
HFD-520/Project Manager/Samanta
HFD-47/Thomas
HFD-47/GCP-II-Files
HFD-47/Reading File
O:\MTT\NDA21918sumDft1.doc
Drafted: MTT: 01/25/06
Reviewed: LKB:
Revised: MTT:

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

/s/

Yolanda Patague
2/1/2006 11:47:12 AM
SECRETARY

Leslie Ball
2/1/2006 01:36:25 PM
MEDICAL OFFICER