

**Mid-Cycle Review Memorandum
OBE/DE Review for Pharmacovigilance Planning**

January 6, 2010
BLA: STN 125354
Coccidioides immitis Spherule-Derived Skin Test Antigen
Allermed Laboratories, Inc.

From: Alexis Mosquera, BSN
Senior Regulatory Review Officer, Therapeutic and Blood Safety Branch
(TBSB), Division of Epidemiology (DE), Office of Biostatistics and
Epidemiology (OBE)

Craig Zinderman, MD, MPH
Medical Officer, TBSB, OBE/DE

Through: Robert P. Wise MD, MPH
Deputy Director, Branch Chief, TBSB OBE/DE

Rickey Wilson, MD, MS, JD
Division Director, OBE/DE

I. Introduction

OBE/DE/TBSB has completed a preliminary review of STN 125354, an original BLA application for *Coccidioides immitis* Spherule-Derived Skin Test Antigen. The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed. Note: The following review contains statements taken directly and/or indirectly from the sponsor's BLA submission. Paragraphs in italics were taken directly from the BLA submission.

Product Background

Coccidioidin SD is indicated for use in the detection of delayed type hypersensitivity (DTH) to *Coccidioides immitis*. A positive skin test to *Coccidioidin SD* indicates prior exposure to *C.immitis*.

Coccidioidin SD is manufactured -----(b)(4)----- saline containing 0.4% phenol as preservative. *Coccidioidin SD* is preserved with 0.4% phenol -----(b)(4)----- . The final product contains 12.7 µg/mL of *C.immitis* antigen. (Summary pp.1-2)

The dose of *Coccidioidin SD* is 1.27µg/0.1 mL administered intradermally on the volar surface of the forearm. The skin is assessed 48 ± 4 hours after administration for induration. Induration of ≥5 mm is considered to be a positive DTH response and indicates prior exposure to *C.immitis*. Induration <5 mm is considered a negative DTH response and indicates absence of prior exposure to *C.immitis*. (Protocol S 104-2 p. 11)

Coccidioidin SD was granted orphan-drug status on December 19, 2007.

Disease

Coccidioidomycosis is a fungus infection which is acquired by the inhalation of the spores of the fungus C.immitis. The disease is usually a self-limiting pulmonary infection characterized by flu-like symptoms. In a small percentage of individuals, the primary pulmonary infection may progress to pneumonia, or disseminate to other parts of the body, including the skin, bones and central nervous system. In some cases the outcome is fatal.

Estimates indicate that four million people live in areas of the U.S. where C.immitis is endemic in the soil. Among naïve persons, the chance of infection is about three percent per year. The longer one resides in an endemic area, the greater the risk of contracting the disease. There are approximately 100,000 new infections each year in the U.S. Most infections occur in Southwestern states of the U.S. (Texas, Southern California, and Arizona). The most common symptoms are fatigue, cough, fever, rash, headache, and joint aches. The usual course of the disease in otherwise healthy people is complete recovery within six months. About five percent of patients develop lung cavities and one to two percent develop disease that disseminates to other parts of the body. Meningitis is the most serious and lethal complication of disseminated disease. (Summary p.1)

While there are no racial or gender differences in susceptibility to primary coccidioidomycosis, differences in risk of disseminated infection do occur. The rate of dissemination in African Americans, Filipinos, Native Americans, Hispanics, and Asians is higher than in other ethnic groups.

C.immitis has become an important cause of opportunistic infections in immunocompromised patients, especially HIV infected patients. Sixty percent of new U.S. cases are asymptomatic. (1)

-----**(b)(4)**-----
-----**(b)(4)**-----

----- is preserved with 0.4% Phenol. According to the

Subjects were 33 to 55 years old with a mean of 44.0 years and were predominantly male (58.3%) and Caucasian (100%). There were no minority groups represented in the study. (ISS table 6)

The safety of *Coccidioidin SD* in all of the three studies was based on the absence of local or systemic reactions. Local reactions that were monitored included the size of the induration response, swelling, itching, pain, blistering and necrosis. Systemic responses monitored included flu-like symptoms, increase heart rate, nausea/cramps, fatigue, weakness, faintness, and difficulty breathing.

II. Safety Assessment

In the three clinical trials a total of 125 subjects received *Coccidioidin SD* (53 with a history of pulmonary coccidioidomycosis, 60 without a history of exposure to *C.immitis*, and 12 with a history of pulmonary histoplasmosis), (Summary Sec. B)

Itching (75% of subjects), swelling (76%), and pain (21%), were the most frequently reported AEs in each of the studies. Other frequently reported AEs included flu-like symptoms (7%) and ulceration (4%). (ISS Sec. III) Table 4 shows the combined adverse events for studies S104-1, S104-2, and S104-3.

Table 4. Combined data for adverse events reported for studies S104-1, S104-2, and S104-3. Table shows the number of subjects with mild, moderate and severe events, and duration of events.

Intensity	Mild (barely noticeable not bothersome)				Moderate (definitely noticeable, discomfort)				Severe (needs medical attention)				Unknown*	Total	%
	0-48 hrs	48-72 hrs	> 72 hrs	Mid-study**	0-48 hrs	48-72 hrs	> 72 hrs	Mid-study	0-48 hrs	48-72 hrs	> 72 hrs	Mid-study			
Adverse Event															
Common															
Itching	20	10	17	2	5	7	29	1	1	0	1	0	1	94	75
Swelling	13	8	34	0	4	10	24	0	0	0	2	0	0	95	76
Pain	8	4	6	0	2	0	5	0	0	0	0	0	1	26	21
Less Common															
Necrosis (ulceration)	2	0	0	1	0	0	0	1	0	0	0	0	1	5	4
Increased heart rate	2	0	1	0	0	1	0	0	0	0	0	0	0	4	3
Weakness	3	0	0	1	1	0	1	0	0	0	0	0	0	6	5
Faintness	1	0	0	1	0	0	0	0	0	0	0	0	0	2	2
Dizziness	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Nausea / Cramps	3	0	1	1	2	0	0	0	0	0	0	0	0	7	6
Flu-like symptoms	3	0	0	0	2	0	2	2	0	0	0	0	0	9	7
Difficulty breathing/ shortness of breath	1	0	0	0	0	0	0	1	0	0	0	0	0	2	2

*Unknown severity and duration. Reported in Investigator's notes.

**Symptom began Mid-Study

In study S104-1 (subjects with a history of histoplasmosis), one subject was dropped from the study due to failure to return to the site for 48 hour reading. There were no dropouts in any of the other studies. There were no dropouts due to AEs. There were no reports of serious AEs. To be considered a serious AE, the event had to: (1) result in death, (2) be life threatening, (3) require hospitalization, (4) result in significant

disability, or (5) pose a threat to the subject's health as judged by the principal investigator. (Summary p.4)

III. Pharmacovigilance Planning

Information in this review is based on preliminary review of the sponsor's Pharmacovigilance Plan (PVP) submitted on October 7, 2009. Comprehensive review of this submission is on-going.

In the PVP, the sponsor proposes the following data collection plans:

Passive Surveillance Plans:

- Expected AE: Include pain, swelling, itching, blistering and necrosis at the injections site, Systemic AE will include increase heart rate, weakness, faintness, dizziness, nausea/cramps, flu-like symptoms, difficulty breathing/shortness of breath, anaphylaxis.
- Unexpected AE: Include any AE that is not included in product labeling. Unexpected AE may be local or systemic reactions to Coccidioidin SD.
- Serious AE: Include events that are life threatening, require hospitalization result in disability or incapacity, considered serious by a medical professional, or result in death.

Active Surveillance Plans

Allermed intends to identify key users of Coccidioidin SD and establish a reporting system regarding the following items of interest:

- a. Intended use of the product
- b. Established diagnosis of coccidioidomycosis
- c. Skin test result at 48 hours
- d. Adverse events, including expected, unexpected, serious AE
- e. Presence of underlying disease except coccidioidomycosis

Allermed proposes to collect information on a quarterly basis during the first 18 months after the product is available for distribution. Allermed intends to collect data from 300 individuals and report a summary of the survey results to CBER within 30 days of each quarter. According to Allermed, the period of survey may be extended if additional information is needed regarding the safety/efficacy of the product. (Response to FDA letter p. 46)

Safety Concerns

1. As noted in the BLA submission, a relatively high proportion (4%) of subjects developed ulcerations at the testing site.

Notable potential AEs include the following:

2. Necrosis and/or infection at the skin test site are possible.
3. As stated in the PVP, a systemic allergic AE can occur following the injection of immunologic agents. Anaphylaxis leading to respiratory/cardiac failure must be considered as a potential risk with any antigenic substance. Because of the relatively small sample size (125 subjects), rare risks like serious allergic reactions might not have been detected in the clinical trials.
4. A positive skin test result does not necessarily mean that a person has been exposed to *C. immitis*, and some positive tests may occur in patients with no actual exposure. The PVP does not address the possibility of false positive or false negative skin tests..

Assessment and Recommendations

1. There do not appear to be serious safety risks identified as AEs in the clinical trials with *Coccidioidin SD*. However, the clinical trial population only included 125 subjects, and was limited to those over 18 and under 65 years old. Once use expands to a larger population, recipients will more commonly have co-morbidities, concomitant medications, or other factors that could lead to adverse events.

2. The following limitations of the studies were noted:

- The number of minority subjects in the study sample was small. Hispanics represented 5.6 percent, African American 4.8 percent, Asians 1.6 percent and Native American/Alaskan 0.8 percent of the total subjects in the study.
- The clinical trials did not include pregnant women, nursing mothers, and subjects over the age of 65 or under the age of 18 year of age. The clinical trials did not include subjects with active medical disease, HIV infection, immunodeficiency disease, alcohol abuse or illicit drugs, influenza-like illness in the past 4 weeks, immunizations in the past 4 weeks, current treatment with corticoid steroids, cytotoxic or immunosuppressive drugs, current atopic or contact dermatitis, psoriasis, erythema nodosum, and urticaria.

3. Limited information was provided on the methodology for the proposed Active Surveillance activity. Allarmed, please clarify or comment on the following:

-Please state the objectives of this activity. Is the surveillance program intended to evaluate safety risks further? If so, what risks?

-Please describe your methods for the selection of individuals and sites as noted in your proposal for postmarketing active surveillance of 300 individuals.

-Please describe the method for collecting the survey data. Does the sponsor intend for participating sites to submit a report for every *Coccidioidin SD* test administered at that site? Alternatively, does the sponsor intend for reports to be submitted only when AEs occur?

-Will Allarmed be able to provide denominator data (number of skin tests administered) at the sites participating in the survey collection?

-There is no opportunity on the form to describe AEs besides those listed.

- There is no opportunity on the form to indicate if the test is administered as part of a clinical evaluation for active coccidioidomycosis.
- The form does not collect data on the age or gender of recipients.
- What is the estimated distribution of the product at the sites that will be participating? -
- How was the participant size of 300 patients chosen?

4. Can Allermmed estimate the extent of use of the product after approval?

Letter Ready Comments

1. Due to the small number of subjects in the clinical trials and the possibility that infrequent serious adverse events such as anaphylaxis may not have been detected in the clinical trials, we agree with your plan to supplement spontaneous adverse event reporting with an active surveillance program. In our review of the proposed pharmacovigilance plan there was limited information regarding the proposed active surveillance activity. Please clarify or comment on the following items:
 - Please state the objectives of this activity. Is the surveillance program intended to evaluate safety risks further? If so, what risks?
 - Please describe your methods for the selection of individuals and sites? Will the program be limited to certain healthcare sites or healthcare providers?
 - Please describe the method for collecting the survey data. Do you intend for participating sites/providers to submit a report for every *Coccidioidin SD* test administered at that site or by that provider? Alternatively, do you intend for reports to be submitted only when AEs occur?
 - Will Allermmed be able to provide denominator data (number of skin tests administered) at the sties participating in the survey collection?
 - There is no opportunity on the form to indicate AEs besides those listed.
 - Question 5 of the reporting form, relates to the intended use of the product. Please clarify what you mean by confirm and detect sensitivity of *Coccidioides immitis*.
 - Please clarify question #7 of the reporting form. Is this question asking if the subject has active coccidioidomycosis and how it was diagnosed or if the subject has a history of the disease and how it was diagnosed?
 - The form does not collect data on the age or gender of recipients.
 - What is the estimated distribution of the product at the sites that will be participating?
 - How was the participant size of 300 patients chosen?

2. Can Allermmed estimate the extent of use of the product after approval?

Bibliography

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