

**Office of Biostatistics and Epidemiology/Division of Epidemiology
Pharmacovigilance Review Memo**

BLA/Supplement Number: 125354

Product Name: Coccidioides immitis Spherule-Derived Skin Test Antigen

Sponsor: Allermid Laboratories, Inc
Indication(s): Detection of delayed type (IV) cell mediated hypersensitivity following pulmonary infection with *Coccidioides immitis*

Date(s): CBER receipt date: 5/14/2009; CBER CR 3/24/2010; Action Due Date: 7/29/2011

Review Priority: NA

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I. Introduction

OBE/DE/TBSB has completed a 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 post-marketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed. Information on clinical studies and safety data in this review is derived from the following documents:

- Clinical summaries presented in the *Spherusol* BLA, Sections 8.2.1 (Integrated Summary of Safety) and 8.3.1 (Integrated Summary of Benefits and Risks)
- Sponsor’s 10/15/2009 amendment entitled “Response to FDA review letter dated 8/4/2009”
- Sponsor’s 6/8/2010 amendment in response to CBER’s 3/26/2010 CR letter (entitled “Spherusol-FDA BL 125354/5 Response to FDA Letter dated March 26, 2010”), items 48-56 and PVP Agreement regarding Spherusol
- Sponsor’s 9/15/2010 amendment (entitled “Response to FDA letter dated August 26,2010, STN BL 125354/006 Sept, 15, 2010”)
- CBER’s incomplete response letters issued on 8/26/2010 and 10/26/2010
- FDA/Applicant Final Meeting Summary dated 2/11/2011 for Type B meeting with Allered on 01/12/2010
- OVR Clinical Review Memorandum dated 3/5/2010, Ann T. Schwartz, MD
- CBER Minutes from Internal Meeting dated 3/23/2011

During the course of this BLA application the sponsor changed the product name from *Coccidioidin SD* to *Spherusol*. Please note that paragraphs in italics were taken directly from the BLA submission.

II. Product Background

2.1 Product

Spherusol is indicated for use as a skin test antigen for the detection of delayed type (IV) cell mediated hypersensitivity following pulmonary infection with *C. immitis*. *Spherusol* should not be used to diagnose active disease or disseminated disease caused by *C. immitis* because it has not been studied for use in diagnosing those conditions (Minutes from Internal Meeting dated 3/23/2011). Note that the proposed indication is under active discussion as part of labeling negotiations and the language may change prior to approval, if approved.

2.2 Regulatory History

-----~~(b)(4)~~-----

The sponsor submitted an original BLA for approval on 5/27/2009. CBER issued a complete Response (CR) to the sponsor on 3/24/2010 citing multiple CMC and clinical issues, including a request for a proposed clinical use of the product and data to support such use. This CR letter included 9 comments on the PVP (Items #48-56), predominantly regarding the sponsor's proposal to conduct a survey of the physicians of 300 patients receiving the product. The sponsor responded to the CR on 6/8/2010, including a revised clinical indication and multiple revisions addressing the PVP comments in the CR letter. CBER did not consider the sponsor's response sufficient to respond to the CR and issued an incomplete response letter on 8/26/2010, primarily citing the need for additional data to support the sponsor's revised indication. This incomplete response letter also requested clarification of the choice of survey sites for the PVP, as well as clarification of the methods for confirming test "sensitivity" in survey patients.

The sponsor filed an amendment on 9/15/2010, reverting the indication back to the original indication ("-----(b)(4)-----") to address the issues identified in CBER's 8/26/2010 incomplete response letter. Regarding the PVP, this amendment identified 4 study sites that the sponsor will use for the active surveillance survey, estimating 40-200 patients per year per site. The amendment also clarified the methods for assessing skin test sensitivity using the survey. CBER issued a 2nd incomplete response letter on 10/26/2010, citing clinical issues and inviting the sponsor to request a meeting for further discussion. On 1/11/2011, in advance of a planned Type B meeting with the sponsor, CBER issued additional questions to the sponsor regarding the product's indication and anticipated uses. On 1/28/2011, the sponsor submitted a written response to CBER's questions from this meeting, restarting the review time clock. The Type B meeting was held via telecom on 2/11/2011.

III. Clinical Studies

Allermed conducted clinical trials including a dose-response study in 2001 and 2002 and a phase III multi-center trial in 2005 through 2007. In the multi-center trial *Coccidioidin SD* was evaluated using three protocols that were designed to address sensitivity and specificity.

In all three studies, subjects were skin tested with five blinded reagents (*Coccidioidin SD* along with four controls: Candin®, Trichophyton Extract, Thimerosal and Placebo) (S104-1 Sec. 4.2, S104-2 Sec. 4.7, S104-3 Sec. 4.2). The five reagents were randomized according to placement on the forearms. The investigational staff and the volunteers were unaware of the location of specific reagents. Each participant was skin tested on Visit # 1 and asked to complete a diary for the next 48 hours. The results of the skin test were read after 48 hours (\pm 4 hours) on Visit # 2. Subjects were asked to continue to keep a diary to monitor possible adverse events (AEs) until they returned to the physician's office one week later. Vital signs were measured and recorded during each visit. (S104-3 Sec. 4.7)

S104-1:

Study S104-1 was a randomized, double blind, multicenter study of *Coccidioidin SD*, conducted in 53 subjects with a history of pulmonary coccidioidomycosis in Arizona and California. (S104-1 Sec. 4.12)

Subjects were 23 to 64 years old with a mean of 43.5 years and were predominantly male (71.6%) and Caucasian (73.5%). Eleven percent of subjects were Hispanic and African American. Other subjects were Asian (1.8%) and Native American/Alaskan (1.8%). (ISS table 6)

S104-2:

Study S104-2, was a randomized, double blind study in 60 persons with no history of coccidioidomycosis or exposure to the fungus conducted in Washington State, where coccidiomycosis is not endemic. Subjects also did not have a history of travel to an endemic area so would be expected to not have been exposed to *C. immitis*. (S104-2 Sec. 4.12)

Subjects were 18 to 54 years old with a mean of 45.0 years and were predominantly female (65%) and Caucasian (96.6%). One Hispanic and one Asian subject were noted in this study. There were no African Americans or Native Americans represented in the study. (ISS table 6)

S104-3:

Study S104-3, was a randomized, double blind study to evaluate the DTH response to *Coccidioidin SD* in 12 persons with a history of pulmonary histoplasmosis. The study was conducted in Nebraska. (S104-3 Sec. 4.12)

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)

IV. Safety Database

Please see the 1/8/2010 DE/PVP Mid-cycle Review Memorandum for full details on the safety database.

4.1 Safety Population

The total safety database consist of 125 subjects among the 3 clinical trials, including 53 subjects with a history of pulmonary coccidioidomycosis, 60 without a history of exposure to *C. immitis*, and 12 with a history of pulmonary histoplasmosis. The subjects were >52% male and >87% Caucasian. Their ages ranged from 18 to 64 years old with none subjects 65 or older.

4.2 Adverse Events

The most frequently observed AEs were Itching (75% of subjects), swelling (76%), and pain (21%). Other frequently reported AEs included flu-like symptoms (7%) and ulceration (4%). (ISS Sec. III)

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.

In their review of the BLA, OVRP identified limitations to evaluation of safety data from study S104-2 and S104-3. In these two studies, the sponsor recorded local adverse reactions, however, these data are cumulative reactions experienced by subjects who received Coccidioidin SD, Candin, and Trichophyton. The sponsor did not identify which of these 3 agents solicited each local reaction. Thus, reviewers were unable to determine whether *Spherusol*, Candin, and /or Trichophyton caused the reactions. (OVRP OVRP Clinical Review Memorandum dated 3/5/2010 by Ann T. Schwartz, MD)

V. Pharmacovigilance Planning

5.1. Safety

The safety of *Spherusol* was evaluated in subjects between the ages of 18-64 years of age. *Spherusol* was not evaluated in persons under the age of 18 and persons over the age of 64. Allermid cited 3 studies (Aronson et al, Grossman et al, and Emmons and Olson) which described the use of skin test antigens of *Coccidioides immitis* in children and elderly persons. According to Allermid the use of *Spherusol* in these populations will not pose unnecessary risk to this subject population. Aronson et al., noted in their study (1-19 years of age) that in most subjects induration to the skin test peaked at 48 hrs and subsided thereafter. They also noted that in more severe reactions, induration persisted for several weeks followed by desquamation and pigmentation at test site. In addition, *Spherusol* was not evaluated in the following populations:

- *Pregnant or lactating women*
- *Active medical disease**
- *Influenza-like illness within the past 4 weeks*
- *Immunizations within the past 4 weeks*
- *Current atopic or contact dermatitis, psoriasis, erythema nodosum, urticaria*
- *Current treatment with corticosteroids, cytotoxic or immunosuppressive drugs*
- *Immunodeficiency disease*
- *HIV infection*
- *Current cavitory or disease*

**Active Medical Disease: Cardiovascular disease, renal insufficiency, chronic respiratory illness, cirrhosis, chronic hepatitis, chronic pancreatitis, chronic diarrhea, malnutrition, malignancy, autoimmune disease, and asthma*

Sponsor notes that racial and ethnic background are not known to cause variation in a cellular response to coccidioidin skin test, however, data regarding the ethnic background of *C. immitis* subjects is not provided in the PVP.

Important potential and identified risks described by Allermid include local reactions with a positive skin test. These local reactions may be mild to moderate and they include: swelling, pain, itching and blistering. These local reactions appear within the first 24-48 hrs and can persist for several days. The sponsor also noted that some individuals may experience increased

heart rate, weakness, faintness, dizziness, nausea, cramps and flu-like symptoms during the first 24 hrs. Allermed noted that these symptoms are transient and would clear without treatment. Other serious potential risks noted by Allermed include anaphylaxis and serious local reactions resulting in necrosis of tissue surrounding the skin test site (these potential serious reactions were not observed during clinical studies).

5.2 Epidemiology

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. There are approximately 100,000 to 150,000 new infections each year in the U.S. However, the vast majority of cases are subclinical. Actual confirmed cases of the disease are reported by the CDCs MMWR, are less than 10,000 annually.

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. Most infections occur in Southwestern states of the U.S. (Texas, Southern California, and Arizona).

5.3 Proposed PV Plan:

-Passive Surveillance

The sponsor describes Allermed's procedures for collecting, documenting, and submission of spontaneously reported expected and unexpected AEs. These procedures and the sponsor's plan for reporting spontaneous AE reports are consistent with regulations in 21CFR600.80.

-Active Surveillance

Study Design

The sponsor proposes to conduct a survey in four endemic areas for coccidioidomycosis to collect information on adverse events and skin test results for a sample of patients. Each participating site will be asked to provide, on a quarterly basis, a completed survey form for all subjects that are skin tested for the first 18 months the product is available for distribution. Survey sites were selected based on the number of cases of coccidioidomycosis that are seen over a 12 month period at each site (40-200 cases per year per site), with the goal of collecting survey information on 300 individuals. (Sponsor's 10/15/2009 amendment entitled "Response to FDA review letter dated 8/4/2009")

Data Collection

The survey forms will collect demographic information (age and gender) on each patient and information on active medical disease (coccidioidomycosis, diabetes, malignancy, etc.) that may interfere with skin test results. The survey form asks respondents to indicate if the patient experienced any AEs from a list of pre-specified AEs and whether they were noted as mild, moderate or severe. In addition, some individuals who received the skin test might also be clinically evaluated for active coccidomycosis. Evaluation of skin test recipients for active disease is not a requested part of the survey or the sponsor's PV activities, however, if an

evaluation is done for clinical reasons, the form will collect the results (i.e., the form will indicate if a subject is diagnosed with active coccidiomycosis and if so, the date of diagnosis and how the coccidiomycosis was diagnosed (serum, tissue, culture, or sputum). The sponsor proposes to send a summary of survey results to CBER within 30 days of each quarter. (Sponsor's 10/15/2009 amendment entitled "Response to FDA review letter dated 8/4/2009"; OVRM Mid-cycle Review dated 3/5/2010; Sponsor's 6/8/2010 amendment entitled "Spherusol-FDA BL 125354/5 Response to FDA Letter dated March 26, 2010"), items 48-56 and PVP Agreement regarding Spherusol)

The sponsors proposed pharmacovigilance study was not requested by FDA and is not mandated as a regulatory requirement or agreed upon commitment. However, the sponsor can consider the following suggestions to improve the proposed survey form:

1. Item # 1 should specify date of report and not date of administration.
2. Item #6 should request a response regarding the method for diagnosing coccidomycosis, the date of diagnosis, and the treatment only if the response to the first part of the question (subject diagnosed with coccdiomycosis?) is yes.
3. The form could ask for concomitant medications.
4. The form could allow for physicians to add serious adverse events not included on the pre-specified list.

Sample Size

Based on the data from studies S104-1, S104-2, S104-3 the sponsor assumes the number of subjects with serious adverse events would range from Zero (0) to no greater than nine (9). In order to detect an excess of adverse events in the postmarketing study, it is designed such that the binomial exact 95% one sided upper confidence limit for a sample of 300 subjects becomes greater than 5% only when the number of serious adverse events is 9 or more.

VI. Assessment and Recommendations

6.1. There were no safety risks identified as AEs in the clinical trials with *Spherusol*. 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. *Spherusol* has not been tested on any special populations, such as pregnant women or immunocompromised individuals. Allarmed should consider analyzing and reporting data from the survey on subjects -----(b)(4)----- years of age.

6.2. We have no requirements for additional surveillance activities based on the available safety data. Allarmed should conduct routine monitoring and reporting of AEs, including submission of 15-day reports for serious, unlabeled AEs and Periodic Update Reports (PSURs), quarterly for the first three years of licensure and yearly thereafter, as required under 21 CFR 600.80. The sponsors proposed pharmacovigilance study was not requested by FDA and is not mandated as a regulatory requirement or agreed upon commitment. We consider this survey to be a study otherwise undertaken by the applicant as per Guidance for Industry: Post-marketing Studies and Clinical Trials-- Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.

VII. Letter Ready Comments

1. You should monitor and report AEs, including submissions of 15-day reports for serious, unlabeled AEs and PAERs, quarterly for the first three years of licensure and yearly thereafter, as required under 21 CFR 600.80.
2. Regarding your proposed post-market survey, you should consider specifically analyzing and reporting survey data on individuals -----(b)(4)----- years of age.
3. Please consider the following suggestions for improvements to the proposed survey form:
 - Item # 1 should specify date of report and not date of administration.
 - Item #6 should request a response regarding the method for diagnosing coccidiomycosis, the date of diagnosis, and the treatment only if the response to the first part of the question (subject diagnosed with coccidiomycosis?) is yes.
 - The form could ask for concomitant medications.
 - The form could allow for physicians to add serious adverse events not included on the pre-specified list.