HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Spherusol safely and effectively. See full prescribing information for Spherusol.

Spherusol®

***Coccidioides immitis* Spherule Derived Skin Test Antigen**

Solution for Intradermal Injection

Initial U.S. Approval:

----------INDICATIONS AND USAGE----------

Spherusol is a skin test antigen indicated for the detection of delayed-type hypersensitivity to *Coccidioides immitis* in individuals with a history of pulmonary coccidioidomycosis. Spherusol is approved for use in individuals 18-64 years of age.

- The use of Spherusol to detect delayed-type hypersensitivity response in a general population with unknown exposure to *C. immitis* has not been evaluated.
- Persons with acute or disseminated coccidioidomycosis may not develop a delayed-type hypersensitivity response to Spherusol.
- Persons with immunodeficiency and a history of coccidioidomycosis may not develop a delayed-type hypersensitivity response to Spherusol. (**1**)

----------DOSAGE AND ADMINISTRATION----------

- A single 0.1 mL intradermal injection. Induration at injection site to be evaluated 48 hours after administration. (**2.1, 2.3**)

----------DOSAGE FORMS AND STRENGTHS----------

- Multi-dose vial (1 mL) containing a solution of spherule-derived *C. immitis* antigen, 1.27 mcg per 0.1 mL. (**3**)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) to Spherusol, or any component of Spherusol or other coccidioidin products. (**4**)

----------WARNINGS AND PRECAUTIONS----------

- Acute hypersensitivity reactions and anaphylaxis have occurred following the administration of other skin test antigens and may occur in individuals following the administration of Spherusol. **(5.1)**
- Patients receiving beta-blocking drugs may be refractive to the usual dose of epinephrine in cases of hypersensitivity. (**5.2**)
- Any condition or agent that impairs or attenuates delayed-type hypersensitivity reactions, including infections and use of immunosuppressive drugs, can potentially cause a false negative reaction to Spherusol. (**5.3**)

----------ADVERSE REACTIONS----------

- The most commonly reported local adverse reactions were itching and swelling (>75%) and pain (>15%) within 7 days of administration. (**6.1**)

To report SUSPECTED ADVERSE REACTIONS, contact Allermed Laboratories, Inc. at (800) 221-2748 or *adverse@allermed.com* or Food and Drug Administration (FDA) at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Corticosteroids and immunosuppressive agents may suppress the response to the skin test. (**7.1**)

----------USE IN SPECIFIC POPULATIONS----------

- The safety and effectiveness of Spherusol in pregnant and nursing women have not been established. (**8.1, 8.3**)

See section 17 for PATIENT COUNSELING INFORMATION

Revised: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Spherusol is a skin test antigen indicated for the detection of delayed-type hypersensitivity to *Coccidioides immitis* in individuals with a history of pulmonary coccidioidomycosis. Spherusol is approved for use in individuals 18-64 years of age.

- The use of Spherusol to detect delayed-type hypersensitivity responses in a general population with unknown exposure to *C. immitis* has not been evaluated.
- Persons with acute or disseminated coccidioidomycosis may not develop a delayed-type hypersensitivity response to Spherusol.
- Persons with immunodeficiency and a history of coccidioidomycosis may not develop a delayed-type hypersensitivity response to Spherusol.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Spherusol is a clear, colorless sterile solution for intradermal administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exists, the skin test antigen should not be administered.

2.2 Administration

Spherusol is administered as a 0.1 mL dose by intradermal injection to the volar surface of the forearm using a tuberculin syringe (0.5 or 1.0 mL) and a ½ inch 26-27 gauge needle. The needle should be inserted bevel side up in the skin at a 15-20 degree angle. Intradermal injection of 0.1 mL Spherusol will result in a bleb 5-10 mm in diameter at the injection site.

2.3 Skin Test Assessment

The injection site should be assessed for induration at 48 hours (±4 hours) following administration. The response to the skin test should be measured by taking the mean of the orthogonal diameters of the area of induration. A mean induration of ≥ 5 mm is considered a positive delayed-type hypersensitivity response to Spherusol.

Repeat administration of Spherusol has not been evaluated.

3 DOSAGE FORMS AND STRENGTHS

Spherusol is a solution for intradermal injection supplied in a 1 mL multi-dose vial. Each 0.1 mL dose contains 1.27 mcg of spherule-derived *Coccidioides immitis* antigen.

4 CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to Spherusol, or any component of Spherusol or other coccidioidin products is a contraindication to administration .

5 WARNINGS AND PRECAUTIONS

5.1 Prevention and Management of Acute Hypersensitivity Reactions

Prior to administration, the healthcare provider should review the medical history for possible skin test sensitivity and previous skin test related adverse reactions to assess the risks and benefits. Immediate hypersensitivity, to include severe systemic reactions, may occur following administration of skin test antigens. Medications and equipment to manage possible anaphylactic reactions should be available for immediate use. Patients should be observed for a minimum of 30 minutes following administration to assess for adverse reactions.

5.2 Patients on Beta Blockers

Patients receiving beta blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis.

5.3 Immunosuppression

Any condition or agent that impairs or attenuates delayed-type hypersensitivity reactions, including infections and use of immunosuppressive drugs, can potentially cause a false negative reaction to Spherusol. [see Drug Interactions (7.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a skin test antigen cannot be directly compared to rates in the clinical trials of another skin test antigen, and may not reflect the rates observed in practice. As with any skin test antigen, there is the possibility that broad use of Spherusol could reveal adverse reactions not observed in clinical trials.

In a double-blinded placebo-controlled clinical trial conducted in areas of the U.S. endemic for *C. immitis* (Bakersfield, CA and Tucson, AZ), 54 adults (23-64 years of age) with a history of pulmonary coccidioidomycosis of at least 45 days duration, diagnosed by clinical findings, radiography and serological and/or mycological evidence of the disease, received a single dose of Spherusol concomitantly with two licensed skin test extracts (Candin and Trichophyton) and two controls (product diluent [thimerosal <0.0001%] and saline). Each intradermal injection of 0.1 mL of reagent was given at pre-determined sites on the right and left forearms. Solicited local adverse reactions and systemic adverse events occurring within 7 days after injection were recorded by study subjects via diary card. These events were also recorded on case report forms (CRFs) by study personnel during clinical visits 48 hours and 7 days following injections. Diary cards and CRFs did not record solicited local reactions by specific site. Local adverse reactions and systemic adverse events that occurred within 7 days were monitored until resolution. Reports of unsolicited adverse events and serious adverse events that occurred within 7 days after administration were collected on the diary cards or reported at study visits.

Table 1 lists the percentage of subjects reporting solicited local reactions (at any site) and solicited systemic adverse events within 7 days following the administration of Spherusol, Candin, Trichophyton, diluent control and placebo control.

Table 1: Frequency of Solicited Local Reactions and Systemic Adverse Events within 7 days of Administration of Spherusol, Candin, Trichophyton, Diluent Control and Saline Control in Subjects with a History of Pulmonary Coccidioidomycosis (N=53)

Symptom	Frequency (%)			
Local*	**Any**	**Mild**	**Moderate**	**Severe**
Itching	85	36	47	2
Swelling	79	36	41	2
Pain	17	13	4	0
Necrosis/Ulceration	4	2	0	2
Systemic				
Increased heart rate	4	2	2	0
Weakness	6	2	4	0
Faintness	0	0	0	0
Dizziness	2	2	0	0
Nausea/cramps	2	2	0	0
Flu-like symptoms	7	2	6	0
Difficulty breathing/shortness of breath	0	0	0	0

Any=Percentage of subjects experiencing adverse event of any intensity; **Mild**= Barely noticeable, not bothersome; **Moderate**= Distinctly noticeable discomfort; **Severe**= Needs medical attention.

*Local reactions occurring at any injection site

Of subjects with severe reactions, one subject required treatment with oral corticosteroids for ulceration and swelling. Based on investigator's determination the reaction was at the site of Trichophyton injection. All severe reactions resolved without sequelae.

During the 7 days following administration two subjects reported unsolicited adverse events: one subject reported joint pain, fatigue, cough, sensitivity at a test site (test site not specified), and one subject with erythema immediately after administration (test site not specified). The intensities of these unsolicited adverse events were not recorded.

No serious adverse events or deaths were reported during the clinical study.

7 DRUG INTERACTIONS

7.1 Corticosteroids and Immunosuppressives

Corticosteroids and immunosuppressive agents may suppress the response to the skin test. Pharmacologic doses of corticosteroids may suppress the response to skin test antigens after two weeks of therapy. The mechanism of suppression is thought to involve a decrease in monocytes and lymphocytes, particularly T-cells. The normal DTH response usually returns to pre-treatment levels within several weeks after steroid therapy is discontinued. [(5)] The use of Spherusol has not been evaluated during or following the use of corticosteroids or immunosuppressive agents.

7.2 Antifungal medications

It is not known if concurrent treatment with antifungal medications interferes with delayed-type hypersensitivity responses to Spherusol in patients with a history of pulmonary coccidioidomycosis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The safety and effectiveness of Spherusol in pregnant women have not been established.

Pregnancy Category C

Animal reproduction studies have not been conducted with Spherusol. It is also not known whether Spherusol can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Spherusol should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

No information is available to assess the effects of Spherusol on childbirth.

8.3 Nursing Mothers

The safety and effectiveness of Spherusol in nursing women have not been established.

It is not known whether Spherusol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Spherusol is administered to a nursing woman. However, because the potential exists for Spherusol to be excreted in human milk, caution should be exercised when administering Spherusol to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Spherusol in the pediatric population have not been established.

8.5 Geriatric Use

The safety and effectiveness of Spherusol have not been established in individuals > 65 years of age.

11 DESCRIPTION

Spherusol is a sterile aqueous solution of extracts of C. *immitis* spherules. The multi-dose vial contains 0.9% sodium chloride and 0.014% sodium borate with 0.4% phenol as a preservative. Residual thimerosal from the manufacturing process is present at a concentration of ≤ 0.0001% (<0.05 mcg mercury/0.1 mL dose). Each 0.1 mL dose contains 1.27 mcg of spherule-derived antigen.

The potency of each lot of Spherusol is determined in sensitized guinea pigs.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In individuals with a history of pulmonary coccidioidomycosis Spherusol is thought to elicit a cellular immune reaction to *C. immitis*, as evidenced by a delayed-type hypersensitivity (DTH) response. The general mechanism of the DTH response is based on the interaction of antigen with CD_4 and CD_8 lymphocytes followed by the secretion of interleukins and other lymphokines from macrophage cells. The release of effector molecules causes endothelial cells lining the blood vessels to become permeable and allows fibrinogen to escape into the surrounding tissue where it is converted to fibrin. The deposition of fibrin and the accumulation of T-cells and monocytes within the extracellular spaces cause the tissue to swell and become indurated. This process is usually detectable in 18 hours and peaks at 48 hours. [(5)]

14 CLINICAL STUDIES

The delayed-type hypersensitivity response following administration of Spherusol was evaluated in one U.S. study which enrolled persons with a history of coccidioidomycosis. Two further U.S. studies enrolled subjects without a history of coccidioidomycosis; in one of these studies subjects had a history of histoplasmosis. In each study, concomitant with Spherusol, two additional skin test extracts, Candin and Trichophyton (positive controls), were administered along with a saline (negative control) and a diluent containing ≤ 0.0001% thimerosal (negative control). All skin tests and controls were administered as 0.1 mL doses in a randomized pattern on the volar surface of the forearms. Investigators and subjects were blinded to identity and placement of skin test antigens and controls. Responses were read at 48 hours (±4 hours) following administration. Induration responses were measured for each test site and recorded as the mean of the orthogonal diameters. A positive skin test was defined as a mean induration of ≥ 5 mm at 48 hours following administration of the antigens or controls. For each subject Spherusol skin test results were considered valid if ≥ 5 mm was observed at the positive control antigen sites and no induration ≥ 5 mm was observed at the negative control sites.

The use of Spherusol to detect delayed-type hypersensitivity response in a general population with unknown exposure to *C. immitis* has not been evaluated.

14.1 Induration Response in Subjects With a History of Pulmonary Coccidioidomycosis

A multicenter, double-blinded study in endemic areas (Bakersfield, CA and Tucson, AZ) enrolled 54 adults with a history of pulmonary coccidioidomycosis diagnosed by radiography, laboratory serologies (e.g., complement fixation, immunodiffusion) and/or culture. Subjects were 23-64 years of age; 28% women; 70% Caucasian, 11 % Hispanic, 2% Asian, 2% Native American and 4% who did not specify race or ethnicity. Of the 51 subjects with valid skin test results, 50 subjects [98.0%; 2-sided 95% CI (89.6%, 100%)] had a mean induration of ≥ 5 mm at the Spherusol injection site. Among subjects with valid skin test results the average size of induration at the Spherusol injection site was 17 mm (range 5 mm-39 mm).

The receipt of concurrent or previous antifungal therapy did not appear to interfere with or accentuate the induration response to Spherusol.

14.2 Induration Response in Subjects Without a History of Pulmonary Coccidioidomycosis or Known Exposure to *C. immitis*

A single site, double-blind study conducted in a non-endemic area for *C. immitis* (Spokane, WA) enrolled 60 adult subjects (18-56 years of age) with no known exposure to *C. immitis* by travel to or residency in an endemic area. Subjects had negative serologies to *C. immitis* by complement fixation, immunodiffusion and/or ELISA. Subjects enrolled in the study were 65% women; 96% Caucasian, 2% Hispanic and 2% Native American. At the 48 hour (± 4 hours) assessment, a total of 55 subjects had valid skin test results (5 subjects had negative skin test results to all reagents and were considered un-interpretable). One subject (1/55) had a 5 mm mean induration response to Spherusol and 54 subjects with demonstrated negative responses (< 5 mm mean induration) to Spherusol. Fifty-four of the 55 subjects with valid

skin test responses [98.2%; 2-sided 95% CI (90.3%, > 99.9%)] demonstrated a negative induration response to Spherusol. When the five subjects who had un-interpretable responses were analyzed as if these responses represented positive reactions to Spherusol, 54 of 60 subjects 90.0% (CI 79.5%, 96.2%) demonstrated a negative induration response.

14.3 Induration Response in Subjects With a History of Pulmonary Histoplasmosis

A single site, double-blind study conducted in a non-endemic area for *C. immitis*, but endemic for *H. capsulatum* (Blair, NE) enrolled 12 adult subjects (33 to 60 years of age) with no known exposure to C. *immitis* by travel to or residency in an endemic area. All subjects had a history of pulmonary Histoplasmosis. Subjects had negative serologies to C. *immitis* by complement fixation, immunodiffusion and/or ELISA. Subjects were 42% women and 100% Caucasian, At the 48 hour (± 4 hours) assessment, all 12 subjects reacted to at least one of the positive controls with ≥ 5mm mean induration and demonstrated negative (< 5mm) induration responses to thimerosal and saline controls. No positive induration responses to Spherusol were observed [1-sided 97.5% CI; (0%, 26.5%)] among subjects who had a previous history of disease caused by *H. capsulatum* and no history of travel to areas endemic for C. *immitis*. These findings support the lack of cross-reaction between the cellular immune responses induced by the two fungal species.

15 REFERENCES

1. Edwards, PQ and Palmer CE. (1957) Prevalence of sensitivity to coccidioidin, with special reference to specific and nonspecific reactions to coccidioidin. Dis Chest. 31:35. 35-60, 1957.
2. Emmons, C.W., Binford, C. H., Ulz, J.P. Kwon-Chung, K.J. Medical Mycology, Leanne Febiger, Philadelphia, Chapter 17, 230, 1977.
3. Emmons CW and Olson BJ. (1945) Studies of the role of fungi in pulmonary disease. I. Cross-reactions with histoplasmin. Pub Health Rep. 60(47):1383.
4. Levine HB, Restrepon A, Eyck DR, and Stevens DA. (1975) Spherulin and coccidioidin: cross-reactions in dermal sensitivity to histoplasmin and paracoccidioidin. Am J Epidemiol. 101(6):512.
5. Zweiman, B. Cell-mediated immunity in health and disease. Allergy Principles and Practices, Mosby, Saint Louis, Chapter 50: 696, 1998.

16 HOW SUPPLIED/STORAGE AND HANDLING

Spherusol is available in 1 mL multidose vial.
NDC 49643-140-01: multi-dose vial.
Store refrigerated at 2° to 8°C (35° to 46°F). Do not freeze. Discard if frozen.
Do not use after expiration date.

17 PATIENT COUNSELING INFORMATION

Patients should be:

- Informed of the potential benefits and risks of skin testing with Spherusol.
- Instructed to report any adverse events to their healthcare provider.

Manufactured by:
Allermed Laboratories, Inc.
San Diego, CA 92111