CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210089Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/16/2020
From	Ravindra K. Kasliwal, Ph. D.
Subject	Cross-Discipline Team Leader Review
NDA #	210089
Applicant	CIS Bio International
Date of Submission	June 05, 2019
PDUFA Goal Date	April 20, 2020[1]
Proprietary Name	Pulmotech™ MAA
Established or Proper Name	Kit for the preparation of technetium Tc 99m albumin aggregated injection
Dosage Form(s)	For injectable suspension
Applicant Proposed Indication(s)/Population(s)	• Lung scintigraphy as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients. • Scintigraphy of peritoneovenous shunt as an aid in the evaluation of its patency in adults.
Applicant Proposed Dosing Regimen(s)	• 1 – 4 mCi for lung scintigraphy • 1-3 mCi for peritoneovenous shunt scintigraphy • 200k – 700k particles, suggested 350 k • 0.025 mCi/kg – 0.050 mCi/kg body weight in pediatrics • 0.2 – 0.5 mCi for newborns • Pediatrics - The number of particles varies with age and weight
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*As indicated above.*
Recommended Dosing Regimen(s) (if applicable)	*As indicated above.*

[1] FDA has listed a goal date that reflects a standard review. As explained in FDA's final guidance on "Interpretation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009" (December 2018), "after March 23, 2020, the Agency will not approve any application submitted under section 505 of the FD&C Act for a biological product subject to the transition provision that is pending or tentatively approved."

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The first technetium Tc 99m albumin aggregated injection drug product (Technescan MAA; NDA 017842) was approved by FDA in 1976. This was approved for scintigraphic imaging of the lungs and as an imaging agent to aid in the evaluation of peritoneovenous (LaVeen) shunt patency. The drug was voluntarily withdrawn in 2009 from the US market by the original NDA holder, Mallinckrodt Nuclear Medicine, LLC. Since the first NDA in 1976, the Agency has approved 8 additional New Drug Applications (NDAs) for technetium Tc 99m albumin aggregated containing products. Currently, however, Draximage MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection) is the only marketed technetium Tc 99m albumin aggregated product in the U.S. market. It is noted that other technetium Tc 99m albumin products have since been discontinued.

The proposed drug product, Pulmotech MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection) has been submitted as a 505(b)(2) NDA, referencing NDA 017881 (Draximage MAA) as the listed drug. The proposed drug product as well as the listed drug are both supplied as multiple-dose vials. It has been determined that even though the formulations between the proposed new drug product and the listed drug are slightly different, the radiolabeled drug is equivalent in dose, and the differences do not have an effect on safety or efficacy of the proposed drug product relative to the listed drug.

The radiolabeled technetium Tc 99m albumin aggregated is routinely used in the indicated nuclear imaging procedures, and the safety and effectiveness as well as the conditions have been well established for more than 30years of clinical use.

The drug is used for pulmonary imaging as an adjunct in the evaluation of pulmonary perfusion in adults and children. The drug is also used in adults in the evaluation of patency of peritoneovenous shunts.

For the recommended intravenous dosages for lung imaging in pediatric patients, estimates of total-body radiation absorbed dose range from 0.3 mGy to 0.6 mGy; the corresponding estimate for a 70-kg adult is 0.6 mGy. For intraperitoneal shunt scintigraphy of a 70-kg adult, total-body absorbed dose is estimated to range from 0.36 mGy to 0.57 mGy, depending on shunt patency. In rare cases, a person may develop an allergic (hypersensitivity) reaction to the drug. Patients with pulmonary hypertension may respond adversely, as the drug functions by mechanically lodging within the terminal precapillary arterioles and capillaries of the lungs following intravenous administration.

2. Background

Pulmotech™MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection), will be supplied as a 15 mL multiple-dose glass vial containing white lyophilized powder. Pulmotech MAA contains macroaggregates of U.S. licensed human serum albumin. The contents of the vial are under nitrogen. Each vial contains 2 mg of albumin aggregated, 7.1 mg of albumin human (soluble), 0.22 mg of maximum total tin (as $SnCl_2 \cdot 2H_2O$), 0.1 mg (minimum) stannous chloride, and 9 mg of sodium chloride. Hydrochloric acid is added for pH adjustment and the pH of the reconstituted solution is between 5 and 7. The kit does not contain any bacteriostatic agent.

The contents of the kit are not for direct administration. They must be radiolabeled with technetium Tc 99m, prior to administration. Pulmotech™MAA when prepared with sodium pertechnetate Tc 99m injection, obtained from a commercially available technetium Tc 99m generator, provides Technetium Tc 99m Albumin Aggregated Injection. While most particles reside in the 10-70 μm range, the particle size distribution of the aggregated albumin is such that not less than 90 percent are 10 to 90 microns in size. There are no aggregated albumin particles with a circular equivalent diameter greater than 150 microns in size. The radiolabeled Pulmotech MAA may be administered intravenously or intraperitoneally.

Radiolabeled Pulmotech MAA (technetium Tc 99m albumin aggregated injection) is a radioactive diagnostic agent indicated for:

- Lung scintigraphy as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.
- Scintigraphy of peritoneovenous shunt as an aid in the evaluation of its patency in adults.

Within 1 to 5 minutes of intravenous injection, over 90 percent of the technetium Tc 99m albumin aggregated particles are trapped in the arterioles and capillaries of the lung. Distribution of aggregated albumin in the lungs is a function of regional pulmonary blood flow, which enables imaging of areas of pulmonary perfusion. Following intraperitoneal administration, the radiopharmaceutical mixes with the peritoneal fluid. Clearance from the peritoneal cavity varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.

The recommended intravenous dose range for adult patients for lung imaging is 37 MBq to 148 MBq (1 mCi to 4 mCi) and 200,000 to 700,000 particles of Technetium Tc 99m Albumin Aggregated Injection. The recommended intraperitoneal dosage range for adult patients for peritoneovenous shunt patency evaluation is 37 MBq to 111 MBq (1 mCi to 3 mCi) and 200,000 to 700,00 particles. Adequate measures should be taken to assure uniform mixing with peritoneal fluid. Serial images of both the shunt and target organ should be obtained and correlated with other clinical findings. Alternatively, the drug may be administered by percutaneous transtubal injection. The recommended percutaneous transtubal dosage range for adult patients is 12 MBq to 37 MBq (0.3 mCi to 1 mCi) in a volume not to exceed 0.5 mL.

The recommended range of particle numbers per single injection is 200,000 to 700,000 in adults with the recommended number of approximately 350,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 mL to 1.9 mL.

In a pre-NDA meeting with the sponsor under IND 132108 on May 3, 2017, the review team disagreed with the sponsor's proposal to market Pulmotech MAA by "reactivating" withdrawn NDA 17842 for Technescan MAA . The review team, however, agreed that the sponsor could submit a 505(b)(2) NDA for Pulmotech MAA that relies, in part, on FDA's finding of safety and effectiveness for Draximage MAA, the listed drug that is currently marketed under NDA 17881.

The review team further clarified that no new clinical data was needed for this proposed 505(b)(2) application. Accordingly, the current submission does not contain clinical data for Pulmotech MAA. The applicant has provided a summary of information from products other than the relied upon listed drug (i.e., other withdrawn or foreign products). This summary did not find any new clinical findings and concluded that there is no new need for clinical data for Pulmotech MAA. Additionally, there is no additional need for supplemental clinical data to establish a "bridge" to the listed drug to support reliance on the Agency's finding of safety and effectiveness for the listed drug.

3. Product Quality

- The application was submitted as a 505(b)(2) NDA, referencing NDA 017-881 (Draximage®MAA) as the listed drug. The proposed drug product as well as the listed drug are supplied as multiple-dose vials. Biopharmaceutics has made a determination that even though the formulation (and component amounts) between the proposed new drug product and the RLD are different the dose of the radiolabeled drug is equivalent, and these differences do not have an effect on safety or efficacy of the proposed drug product relative to the listed drug.

- The applicant utilizes FDA-approved US sourced Albumin (b) (4) for the manufacture of macroaggregated (MAA) particles, and for use as an excipient in the drug product. (b) (4) (b) (4) and has been determined to be acceptable for use.

- Product quality has determined that the components used for the drug product and their quality are adequate and have been qualified through successful manufacture and stability studies. The drug product specifications and the analytical procedures are adequate to control the identity, strength, purity and quality of the drug product. The control strategy for impurities (organic, (b) (4) and elemental impurities) is adequate.

- Manufacturing and controls are adequately defined. The drug product manufacturing process and procedures are adequate for the manufacture of proposed sterile, (b) (4) (b) (4), lyophilized drug product. The container and closure system (clear glass vial

with aluminum crimp sealed stopper) is adequate to maintain the quality, stability and sterility of the drug product throughout the shelf-life of the product.

- The drug product manufacturing facility was inspected and has an acceptable CGMP status for the manufacture of proposed sterile, (b) (4) lyophilized drug product. Other manufacturing, testing, labeling and packaging facilities have acceptable CGMP status.

- The drug product (kit) can be acceptably radiolabeled with sodium pertechnetate Tc 99m injection solution obtained from (b) (4) The available long-term stability data supports a **12-months expiration dating period for Pulmotech™MAA when stored at 2 to 25° C (36 to 77°F)**.

- Radiolabeled product's stability data supports labeling statements "**radiolabel with ≤ 185 mCi of sodium pertechnetate Tc 99m injection in 2-13 mL volume**" and "**Store radiolabeled product in a refrigerator at 2-8°C and use within 18 hours of preparation"**.

4. Nonclinical Pharmacology/Toxicology

The applicant has relied on a "bridge" to the listed drug (NDA 017-88; Draximage MAA) to support reliance on the Agency's finding of safety and efficacy for the listed drug. The critical features of technetium Tc 99m albumin aggregated, besides the radioactivity amount (which is the same), that affect the pharmacodynamics, pharmacokinetics, and toxicology are the particle size characteristics and the total number of administered particles. The particle size characteristics of this proposed product are consistent with the listed drug and with the accepted particles distribution in that most of the particles are in the 10-90μm range (needed for product performance), and there are no particles with a circular equivalent diameter larger than 150μm that could contribute to undesirable adverse effects.

The primary mechanism of action for technetium Tc 99m albumin aggregated involves radiolabeled particles getting mechanically lodged within the terminal precapillary arterioles and capillaries of the lungs following intravenous administration. This allows lung scintigraphic imaging for up to several hours. The entrapped particles are slowly cleared through mechanical fragmentation, induced by changes in pressure and flow in the lungs. Fragmented particles clear the lung capillaries, enter the blood pool, and are taken up by the mononuclear phagocytic system cells of the liver and spleen. These smaller particles are finally metabolized releasing free pertechnetate which is excreted in the urine.

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether technetium Tc 99m albumin aggregated affects fertility in males or females.

5. Clinical Pharmacology

Within 1 to 5 minutes of intravenous injection, over 90 percent of the technetium Tc 99m albumin aggregated particles are trapped in the arterioles and capillaries of the lung.

Following intraperitoneal administration of Technetium Tc 99m Albumin Aggregated Injection, the radiopharmaceutical mixes with the peritoneal fluid. Clearance from the peritoneal cavity varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.

Organ selectivity is a direct result of particle size. At 10 microns and below, the albumin aggregates are taken up by the reticuloendothelial system. Above 10 to 15 microns, the aggregates become lodged in the lung capillaries by a purely mechanical process. Distribution of aggregated albumin in the lungs is a function of regional pulmonary blood flow. The albumin aggregated is sufficiently fragile for the capillary micro-occlusion to be temporary. Erosion and fragmentation reduce the particle size, allowing passage of the aggregates through the pulmonary alveolar capillary bed. The fragments then accumulate in the reticuloendothelial system.

Elimination of the Technetium Tc 99m Albumin Aggregates from the normal and abnormal human lungs occurs with a biological half-life of 10.8 hours (range 6.9 to 19 hours).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The NDA was submitted as a 505(b)(2) application and the applicant has relied on a "bridge" to a listed drug (NDA 017-881; Draximage® MAA) to support reliance on the Agency's finding of safety and effectiveness for the listed drug. The application does not contain any new clinical data. Based on the "bridge", it was determined that the prescribing information (PI) for the relied upon listed drug was relevant to Pulmotech MAA. It was noted that the Pulmotech MAA prescribing information is in Physician Labeling Rule (PLR) format, while the prescribing information of the listed drug is not in PLR format. Additionally, the Pulmotech MAA prescribing information is in the Pregnancy and Lactation Labeling Rule (PLLR) format, while the listed drug is not. A comparison of the PI indicated the following:

- The proposed indication for Pulmotech MAA is sufficiently similar to the listed drug relied upon.
- The dosage, in terms of the radioactivity dose and the number of macroaggregated particles, is the same.
- The manner and the route of administration of the two products is the same.
- The radiation dose received from the product is the same.
- The contraindications for Pulmotech MAA are adequate from a clinical perspective. In Pulmotech MAA prescribing information, revisions have been recommended for clarity and / or compliance with the labeling rules.
- Warnings and precautions (as related to the pulmonary hypertension, hypersensitivity reactions and radiation risks) for Pulmotech MAA are adequate from a clinical perspective.

In Pulmotech MAA prescribing information, revisions have been recommended for clarity and / or compliance with the labeling rules.

- The adverse reactions noted for Pulmotech MAA are adequate from a clinical perspective. In Pulmotech MAA prescribing information, revisions have been recommended for clarity and / or compliance with the labeling rules.
- The product's use in specific population (in pregnant or lactating women, in pediatric patients) is adequate from a clinical perspective. In Pulmotech MAA prescribing information, revisions have been recommended for clarity and / or compliance with the labeling rules.
- The listed drug's prescribing information does not contain patient counseling information. Consistent with currently applicable Physician Labeling Rule (PLR) format, patient counseling information concerning adequate hydration to reduce radiation exposure has been added to the PI.
- The dosimetry tables (pediatrics and adults) are also acceptable because comparison of 2015 ICRP-based dosimetry demonstrated no clinically significant differences with that from the listed drug relied upon (Draximage MAA).

8. Safety

Serious adverse reactions have been reported in patients with pulmonary hypertension after Technetium Tc 99m Albumin Aggregated Injection. The prescribing information, consistent with the listed drug, advises to assess patients for history or signs of pulmonary hypertension, administer the lowest possible number of particles, have emergency resuscitation equipment available and monitor patients for adverse reactions.

This being a human serum albumin and denatured macroaggregated albumin product, serious hypersensitivity reactions, including deaths, have been reported in patients who have hypersensitivity to such products. The prescribing information, consistent with the listed drug, advises health care provider to obtain a history of allergy or hypersensitivity reactions and always have emergency resuscitation equipment and trained personnel available prior to administration of Technetium Tc 99m Albumin Aggregated Injection. Additionally, advise to monitor all patients for hypersensitivity reactions is included.

Pulmotech MAA, subsequent to reconstitution with technetium Tc 99m injection solution, is radioactive and appropriate measures should be taken to minimize radiation exposure to the patient and to insure minimum radiation exposure to occupational workers. To this end, the patients should be advised to drink a sufficient amount of water to ensure adequate hydration before their study and urge them to drink water and urinate as often as possible during the first hours following the administration of Technetium Tc 99m Albumin Aggregated Injection in order to reduce radiation exposure.

9. Advisory Committee Meeting

There was no advisory committee meeting for this application.

10. Pediatrics

Pediatrics use is the same as the listed drug for this 505 (b)(2) NDA. Technetium Tc 99m Albumin Aggregated Injection is indicated for lung scintigraphy as an adjunct in the evaluation of pulmonary perfusion in pediatric patients. The safety profile of Technetium Tc99m Albumin Aggregated Injection is similar to the one in adults.

In pediatric patients, the recommended intravenous dose for perfusion lung imaging is in the range of 0.925 MBq/kg to 1.85 MBq/kg (25 μCi/kg to 50 μCi/kg) of body weight; a usual dose is 1.11 MBq/kg (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 MBq to18.5 MBq (200 μCi to 500 μCi). Not less than the minimum dose of 7.4 MBq (200 μCi) should be employed for this procedure. The number of particles varies with age and weight and should be kept as low as possible.

Pediatric Patients: Particle Number and Dose for Lung Scintigraphy

Age	Newborn		1 year		5 years		10 years		15 years	
Weight (kg)	3.5		12.1		20.3		33.5		55	
Maximal recommended dose	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi
	18.5	0.5	22.2	0.6	37	1	62.9	1.7	103.6	2.8
Range of particles administered	10,000 to 50,000		50,000 to 150,000		200,000 to 300,000		200,000 to 300,000		200,000 to 700,000	

11. Other Relevant Regulatory Issues: None.

12. Labeling

The relied upon listed drug's prescribing information is not in the currently required Physician Labeling Rule (PLR) format. While the Pulmotech MAA drug relies upon the Agency's finding of the safety and effectiveness for Draximage MAA (NDA 017-881), the prescribing information for the proposed drug should be in conformance with the PLR and PLLR format. Accordingly, necessary updates related to dosing and administration, patient counseling, contraindications, warning and precautions, adverse reactions, pregnancy, lactation and pediatric use have been implemented.

The proposed drug product is administered in a hospital or a diagnostic imaging center by a health care provider. It is not self-administered and hence there is no patient labeling.

Carton and container labeling changes have been made, so that the labels conform to current requirements.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

None.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

None.

14. Recommended Comments to the Applicant

None.

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/s/

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