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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

Application Number	NDA 210089 SDN 3
Letter Date of Submission	June 11, 2019
Product Name (Trade and generic, code)	Pulmotech MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection)
Route of Administration	Intravenous and Intra-peritoneovenous
Proposed Indication	Technetium Tc 99m Albumin Aggregated Injection: • Is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients. • May be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (b) (4) shunt patency.
Submission Type	505(b)(2)
Related Applications	None
Sponsor	CIS Bio International
Prior Reviews (Application number, Submission type, Date)	None

Executive Summary

CIS Bio International submitted an original New Drug Application (NDA) pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Pulmotech™ MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection). The applicant identified DraxImage MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection) as the listed drug relied upon. DraxImage MAA (NDA 017881) is held by Jubilant DraxImage Inc.

The applicant is seeking the same indications as the approved label for Draximage MAA application (NDA 017881). The approved indications for DraxImage MAA are:

- Technetium Tc 99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.
- Technetium Tc 99m Albumin Aggregated Injection may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (LeVeen) shunt patency.

There were no clinical pharmacology studies conducted by the applicant for the support of this application. The applicant has cited literature reports and professional societies recommendations to support clinical pharmacology section of NDA. The literature reports and professional societies recommendations are supportive of the NDA but are not essential for the approval of the proposed product.

Recommendation: The application is approvable from a clinical pharmacology perspective.

Summary of Clinical Pharmacology Findings
Human PK
There were no specific clinical pharmacology studies performed by the applicant. The mechanism of action of MAA preparations is the physical entrapment of particles too large to transit a capillary network. The clinical studies described in the literature are supportive of the initial high extraction efficiency of Tc-99m MAA in the lungs.

Immediately following intravenous injection, more than (b)(4)% of the Tc-99m labeled macroaggregated albumin particles are trapped in the pulmonary alveolar capillary bed. The imaging procedure can thus be started as soon as the injection is complete. Assuming that a sufficient number of radioactive particles have been used, the distribution of radioactive aggregated particles in the normally perfused lung is uniform throughout the vascular bed, and will produce a uniform image. Areas of reduced perfusion will be revealed by a corresponding decreased accumulation of the radioactive particles, and are imaged as areas of reduced photon density.

Injection of preparations containing particles greater than 10-15 μ are almost 100% retained in the lungs during the first 1-5 minutes following injection into a peripheral vein. The MAA particles themselves are known to be fragile and become mechanically fragmented and eroded until they become small enough to clear the capillaries, and then transfer to the circulating blood.

These smaller particles become phagocytized by the Kupffer cells of the liver and spleen where they are further metabolized resulting in the release of free pertechnetate that distributes in the body as the pertechnetate ion that is primarily excreted by the kidney.

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 are then accumulated by 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 - 19 hours, n=5).

Reviewer's Comment: Based on the above PK summary provided by the applicant, it can be concluded that particle size and number of particles play key role in determining the PK, biodistribution and the biological half-life in the lungs: smaller particles result in shorter T1/2 than larger particles.

The pharmacokinetics and biodistribution of Technetium Tc 99m Albumin Aggregated depends on four important factors 1) Dose 2) Number of particles 3) particle size 4) Formulation. These factors and comparison of the test drug (Pulmotech) with the listed drug relied upon (DraxImage MAA) are described in this review.

1) Dose

The proposed intravenous dose range for the average (70 kg) adult patient for lung imaging is 37 to 148 MBq (1 to 4 mCi). The proposed intraperitoneal dosage range used in the average patient (70 kg) for peritoneovenous (b) (4) shunt patency evaluation is 37 to 111 MBq (1 to 3 mCi). However, in pediatric patients, the suggested intravenous dose for perfusion lung imaging is in the range of 0.925 to 1.85 MBq per kilogram (25 to 50 μCi/kg) of body weight. In newborns, the administered dose should be 7.4 to 18.5 MBq (200 to 500 μCi).

Reviewer's Comment: This dose is acceptable as it is based on the approved labeling for DraxImage MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection). The proposed dosing is also supported by historical clinical use of this agent as also described in the literature.

2 and 3) Number of Particles and Particle Size

In the lung of an adult there are approximately 280 billion capillaries and 300 million arterioles. Therefore, following the injection of Tc-99m MAA, which typically contain about 350,000 (range 200,000 to 700,000) particles, and depending on the particle size distribution relative to regional blood flow, roughly one out of every one million capillaries (diameter < 20μm) and one out of every 1,000 arterioles (= 0.1%) (diameter > 20μm) become temporarily occluded.

The recommended number of particles injected to an adult normal patient range from 200,000-700,000 (DraxImage Labeling). In order to achieve good imaging quality, the literature recommends at least 60,000 particles; however, a maximum of 700,000 particles is the recommended limit due to safety concerns. Therefore, even if the maximum number of particles

were injected under the least favorable assumption of a diameter > 20μm for all particles, only 700,000 out of 300,000,000 = 0.23% of the arterioles in an otherwise normal healthy adult lung would be occluded by the particles.

Radiolabeled MAA is a particulate suspension prepared by mild heat denaturation of human serum albumin using conditions to control the particle size to between 10 and about 90 microns. At least 90% of the particles in Tc99m-MAA preparations would need to range between 10 and 90 microns to meet the USP monograph. Fewer than 10% of the particles can be <10 μm or greater than 90 μm; none are permitted to be greater than 150 μm. Organ selectivity is a direct result of particle size. Below 1 to 10 micrometers, the material is taken up by the reticuloendothelial system. Above 10 micrometers, the aggregates become lodged in the lung by a purely mechanical process. Distribution of particles in the lungs is a function of regional pulmonary blood flow.

The proposed product is a multiple dose vial that contains 2.0 mg of MAA and a total number of particles between 2 million to (b)(4) million particles. The listed drug relied upon is also supplied as multiple dose vial, contains 2.5 mg MAA and a total number of particles that ranges between 3 million to (b)(4) million particles. In each case, the exact number of particles found in the batch are provided on the vial label. Technetium Tc 99m MAA injection is administered based on the number of particles (and radioactivity). In both drugs, the proposed product and the listed drug relied upon, the recommended dose for ^{99m}Tc-MAA in adults is 200,000-700,000, with the suggested number being 350,000. Both DraxImage MAA and the proposed CIS BIO product are prepared in a multi-dose format.

Reviewer's Comment: Particle numbers injected in a patient is one of the most important criteria for the performance of Tc-99m-MAA clinically. The package insert of both Pulmotech MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection) and DraxImage MAA provides methodology to prepare the radiolabeled drug, by adding radioactivity and volume of sodium pertechnetate technetium Tc 99m injection so that the patient dose (volume to be injected) will contain particles between 200,000 to 700,000. Therefore, the radiolabeled product will be similar in both cases. Thus, it is expected that the listed drug relied upon and the test drug will perform similarly.

4) Formulations

A comparison of the formulation for the proposed (test) product and the listed drug relied upon (DraxImage MAA) is given in **Table 1**.

Table 1. Comparison of Batch Formula for Proposed Cis Bio US AAI (Pulmotech) and DraxImage MAA

Component	Proposed CIS Bio US AAI (Tc-99m MAA)	DraxImage MAA
Macroaggregated Albumin (MAA)	2 mg	2.5 mg
Number of particles per Vial	2-4 x 10^6	Not specified in current labeling, Actual number of particles provided for each batch
Stannous chloride (b) (4)	100 µg	≥60 µg
Total tin (stannous & Stannic chloride)	Not specified	110 µg
Human serum albumin (HSA)	7 mg	5 mg
(b) (4)		
Sodium chloride	9 mg	1.2 mg
HCl/NaOH	Adjust pH	Adjust pH

The proposed product contains 2 mg of macroaggregated albumin (MAA) compared to 2.5 mg in the listed drug relied upon. It also contains a slightly different amounts of excipients, namely soluble albumin human (7 mg/vial compared to 5 mg/vial in the listed drug relied upon), stannous chloride dihydrate (100 microgram mg/vial compared to ≥ 60 micrograms/vial in the listed drug relied upon), and sodium chloride (9 mg/vial compared to 1.2 mg/vial in the listed drug relied upon). However, these differences, between the proposed product and the listed drug relied upon, are not expected to affect the in vivo performance for the reasons given below for differing content of (b) (4) MAA particle and stannous chloride content.

(b) (4) Macroaggregated Albumin (MAA) content:
Although the overall mass of (b) (4) MAA is higher in the listed drug relied upon, the mass of MAA delivered normalized over a dose of 350,000 particles is between (b) (4) for DraxImage MAA and the Cis Bio proposed product respectively. The range of MAA administered in the proposed product falls within the range of the listed drug relied upon and is inconsequential to the performance of the product. The drug safety and effectiveness depend upon the number of particles trapped in the lung capillaries and the amount of radioactivity associated with them which provides the image. As discussed above the number of particles injected are within the recommended range for two formulations. Thus, the in vivo performance (efficacy) and safety are expected to be equivalent.

Stannous chloride content:
Radiopharmaceutical kits for labeling with Tc-99m eluate contain stannous (b) (4) . The lower valence state Tc 99m physico-chemically binds to the MAA particles. As seen in the Table 1, the proposed product has a higher stannous content required (100 microgram vs 60 micrograms in the listed drug relied upon). The stannous chloride amount in the proposed product provides sufficient reduction of Tc 99m and radiolabeling of the MAA particles over shelf life of the product. Therefore, amount of stannous ion is not expected to have an impact on performance or the safety of the product.

Reviewer's Comment: There are minor differences between the listed drug relied upon and Curium (Cis Bio) products as listed above and shown in Table 1. The two most important attributes for the proper performance of Tc-99m-MAA are the number of particles to be injected in patient and the particle size. As indicated above these attributes are similar for two products. The differences in the amounts of stannous MAA particles and stannous chloride concentration would not make a clinically significant difference in efficacy or safety of the drug.

Signature

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