CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210089Orig1s000

CLINICAL REVIEW(S)

March 17, 2020

MEMORANDUM

Division of Medical Imaging and Radiation Medicine

NDA: 210089

Applicant: CIS Bio International

Product: Pulmotech MAA

From: Libero, Marzella MD, PhD

I concur with the cross-discipline team leader (CDTL) Dr. Kasliwal and with the NDA review team's risk versus benefit assessment for Technetium Tc 99m Albumin Aggregated Injection. I concur with the unanimous recommendation by the NDA reviewers that the application be approved.

With regard to the dosimetric tables in the labeling, I agree with the following considerations:

- The more recent methodology (based on ICRP Publication 128) for assessment of radiation absorbed dose at the organ level offers the potential for more accurate estimates of dose than are provided in the present labeling.
- The numerical differences between the dose estimates presented in the labeling and the estimates obtained with the more recent methodology are generally small, and the variability associated with estimated values is not explicitly specified in either the labeling or in the ICRP Publication 128 tables for Tc-99m albumin aggregated.
- The stochastic risk of carcinogenesis posed by radiation absorbed doses associated with Tc-99m albumin aggregated is low, and the uncertainty around the estimates of this risk is high and would exceed any postulated improvement in accuracy of the radiation dose estimates using ICRP Publication 128.
- Radiation-attributable lifetime risk (per unit absorbed dose) for cancer incidence or mortality is derived from epidemiological studies involving large population cohorts. These risk estimates are generally uncertain by a factor of 2 to 3. For Tc 99m albumin aggregated the potential improvement in accuracy of organ absorbed-dose values derived from ICRP Publication 128 and applied as input for radiation-attributable lifetime cancer-risk projections for an individual patient would not compensate for the uncertainty in the epidemiologically-based values. In this circumstance of potentially improved accuracy of organ-dose estimates without corresponding improvement in the accuracy of assessment of radiation risk, ICRP Publication 128 dose values would provide no difference in the clinical consideration of the radiation safety and risk for the product affecting its use.

Therefore, I agree with the radiation absorbed doses presented in the labeling and summarized in the CDTL review.

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/s/

LIBERO L MARZELLA
03/17/2020 05:23:01 PM

DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DMIRM)
Medical Officer Memo for 505(b)(2) NDA
(No Module 5 clinical data submitted)

NDA: 210089
SDN: 3
Product: Technetium Tc 99m Albumin (Pulmotech MAA)
Applicant: CIS BIO INTERNATIONAL C/O CURIUM US LLC
Subject: memo of the primary NDA review
The listed drug relied upon: Draximage MAA (Technetium Tc 99m Albumin Aggregated, NDA 17881) [1]
Submission received: 06/11/2019

Reviewer: Qi Feng, MD, PhD
Review finished date: 3/9/2020

Executive Summary:
This submission is a 505(b)(2) NDA for Pulmotech MAA, a radioactive diagnostic agent with a proposed indication 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.

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 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 505(b)(2) approval pathway may be used for a proposed Technetium Tc99m Albumin Aggregated Injection product that is demonstrated to be sufficiently similar to a listed drug to permit reliance, where scientifically justified, on FDA's finding of safety and/or effectiveness for the listed drug to support approval of an NDA. A demonstration of similarity to the listed drug may include, for example, comparative physico-chemical tests and bioassay, nonclinical data (which may include bridging toxicology studies), pharmacokinetic (PK) / pharmacodynamic (PD) data, and clinical data (which may include an assessment of immunogenicity."

The review team further clarified that no new clinical data was needed:

> "You may submit a 505(b)(2) application that includes no new clinical data."

Accordingly, the current submission contains no clinical data for Pulmotech MAA. In addition, the applicant's summary of information from products other than the listed drug relied upon (i.e., other withdrawn or foreign products) suggests no new clinical findings, no new need for Pulmotech MAA clinical data, and no rationale for review of new clinical data or new clinical review for determination of whether the applicant has demonstrated sufficient similarity to the listed drug for reliance on FDA's finding that the listed drug is safe and effective.

During the review cycle, the clinical review team thus served in a supportive role primarily focused on labeling.

Review

There are some labeling format differences between the proposed Pulmotech MAA and the listed drug relied upon (Draximage MAA). The Pulmotech MAA labeling is in Physician Labeling Rule (PLR) format, but the listed drug relied upon is not. The Pulmotech MAA label is in Pregnancy and Lactation Labeling Rule (PLLR) format, but the listed drug relied upon is not. A full review of the clinically related label sections has been performed; see summary table below:

Comparison between the Labels of Pulmotech MAA and Draximage MAA

Label Section	Draximage MAA (Listed drug relied upon)	Pulmotech MAA
1 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. 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.	Sufficiently similar from clinical perspective
2.1 Dosage and Administration	1 - 4 mCi for lung scan	Same
	1 - 3 mCi for LeVeen shunt	
	200 k to 700 k particles, suggested 350 k	
	0.2 - 0.5 mCi for pediatric	
2.2 Radiation Dosimetry	See dosimetry table below	
4 Contraindications	... should not be administered to patients with severe pulmonary hypertension. ... contraindicated in persons with a history of hypersensitivity reactions to products containing human serum albumin.	Adequate from clinical perspective, with additional FDA-to-applicant revision recommended for clarity and/or compliance with labeling rules.
5 Warnings and Precautions		
5.1 Pulmonary Hypertension	The literature contains reports of deaths occurring after the administration of albumin aggregated to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or idiosyncratic reactions to preparations of Technetium Tc 99m Albumin Aggregated have been reported.	Adequate from clinical perspective, with additional FDA-to-applicant revision recommended for clarity and/or compliance with labeling rules.
5.2 Hypersensitivity Reactions	Hypersensitivity reactions are possible whenever protein-containing materials such as pertechnetate labeled albumin aggregated are used in man.	
5.3 Radiation Risks	Once sodium pertechnetate Tc-99m is added to the vial, appropriate safety measures must be used to minimize radiation exposure to clinical personnel. Care must also be taken to minimize the radiation exposure to patients in a manner consistent with proper patient management.	
6 ADVERSE REACTIONS	The literature contains reports of deaths occurring after the administration of albumin aggregated to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or idiosyncratic reactions to preparations of Technetium Tc 99m Albumin Aggregated have been reported.	Adequate from clinical perspective, with additional FDA-to-applicant revision recommended for clarity and/or compliance with labeling rules.

Label Section	Draximage MAA (Listed drug relied upon)	Pulmotech MAA
8 USE IN SPECIFIC POPULATIONS		
8.1 Pregnancy	Pregnancy Category C Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Albumin Aggregated Injection. It is also not known whether Technetium Tc 99m Albumin Aggregated Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Albumin Aggregated Injection should be given to a pregnant woman only if clearly needed.	Adequate from clinical perspective, with additional FDA-to-applicant revision recommended for clarity and/or compliance with labeling rules.
8.2 Lactation	Nursing Mothers Technetium Tc-99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feedings.	
8.3 Pediatric Use	The lowest possible number of particles should be used in right-to-left shunting, in neonates, and in severe pulmonary disease.	
17 PATIENT COUNSELING INFORMATION	None	Adequate Hydration in order to reduce radiation exposure. Acceptable from clinical perspective, with additional FDA-to-applicant revision recommended for clarity and/or compliance with labeling rules.

The dosimetry tables 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). See also health physicist review memo from Stanley Stern.

Pediatric Radiation Dose from Tc 99m MAA for Lung Imaging

Age	Newborn			1 year			5 years			10 years			15 years			Comment
Weight (kg)	3.5			12.1			20.3			33.5			55			
	Draximage	Pulmotech	ICRP 2015	Draximage	Pulmotech	ICRP 2015	Draximage	Pulmotech	ICRP 2015	Draximage	Pulmotech	ICRP 2015	Draximage	Pulmotech	ICRP 2015	
ORGANS																Comparison of 2015 ICRP-based dosimetry demonstrated no clinically significant differences with that from the RLD.
Total body	0.6	0.6	0.6	0.3	0.3	0.3	0.31	0.31	0.31	0.48	0.48	0.48	0.41	0.41	0.41	
Lungs	19	19	19	6.6	6.6	8.7	5.8	5.8	7.4	8.7	8.7	8.2	7.7	7.7	10	
Liver	1.4	1.4	1.4	0.6	0.6	1.6	0.62	0.62	1.6	1.8	1.8	1.9	1.2	1.2	2.2	
Bladder wall	2.1	2.1	2.1	1.5	1.5	0.67	3.1	3.1	0.59	3.9	3.9	0.88	4.1	4.1	1.1	
Ovaries	0.38	0.38	0.38	0.2	0.2	0.22	0.19	0.19	0.2	0.44	0.44	0.22	0.41	0.41	0.24	
Testes	0.31	0.31	0.31	0.13	0.13	0.14	0.19	0.19	0.12	0.2	0.2	0.14	0.36	0.36	0.15	

Absorbed Radiation Doses

	Draximage MAA	Pulmotech MAA	ICRP 2015	Comment
	mGy/148 MBq	mGy/148 MBq	mGy/148 MBq	
Total body	0.6	0.6	0.6	Comparison of 2015 ICRP-based dosimetry demonstrated no clinically significant differences with that from the RLD.
Lung	8.8	8.8	9.8	
Liver	0.72	0.72	2.4	
Spleen	0.68	0.68	0.61	
Kidney	0.44	0.44	0.55	
Bladder wall				
2 hr void	1.2	1.2	1.3	
4.8 hr void	2.2	2.2	2.2	
Testes				
2 hr void	0.24	0.24	0.16	
4.8 hr void	0.26	0.26	0.26	
Ovaries				
2 hr void	0.3	0.3	0.27	
4.8 hr void	0.34	0.34	0.34	

Clinical Concluding Remarks:

If the review team finds that the applicant has submitted CMC data to demonstrate sufficient similarity between Pulmotech MAA and Draximage MAA, the clinical review team agrees that no new clinical data beyond reliance on FDA's finding of safety and effectiveness for Draximage MAA is needed to recommend approval of Pulmotech MAA for the same indications, pending ongoing labeling negotiation.

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/s/

QI FENG
03/12/2020 04:42:44 PM

ANTHONY F FOTENOS
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