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APPLICATION NUMBER:

210089Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM TO FILE

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210089
Supporting document/s:	SDN-3; SDN-12
NDA submission date:	11 June 2019
Review completion date:	11 March 2020
Product:	Pulmotech MAA (kit for the Preparation of Technetium Tc 99m Albumin)
Indication:	Lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients; in adults as an imaging agent to aid in the evaluation of the peritoneovenous (b) (4) shunt patency.
Sponsor:	CIS Bio International C/O Curium US LLC Route Nationale 306 Saclay BP 32 Gif-sur-Yvette, CEDEX, France 91192
Review Division:	Division of Medical Imaging Products
Reviewer:	Jonathan E. Cohen, Ph.D.
Supervisor/Team Leader:	Adebayo Laniyonu, Ph.D.
Division Director:	Libero (Louis) Marzella, M.D., Ph.D.
Project Manager:	Alberta E. Davis-Warren

Template Version: February 13, 2017

Nonclinical Review

Pulmotech MAA is a kit for the preparation of Technetium Tc 99m (^{99m}Tc) radiolabeled macroaggregated albumin. The proposed indication is for "Lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients; in adults as an imaging agent to aid in the evaluation of the peritoneovenous (b) (4) shunt patency". The NDA submission from the Applicant, CIS Bio International, is a 505(b)(2) application for Pulmotech MAA and will rely on FDA's finding of safety and effectiveness for Draximage MAA (NDA 017-881), the listed drug relied upon.

Draximage MAA (NDA 017-881) is the only currently marketed kit for the preparation of Technetium Tc 99m macroaggregated albumin (MAA). TechneScan MAA (NDA 017-842) originally approved in 1976 for (b) (4) was voluntarily withdrawn in 2009 from the US market by the NDA holder, Mallinckrodt Nuclear Medicine, LLC. Mallinckrodt Nuclear Medicine, LLC was acquired by IBA Molecular in 2017 and renamed Curium.

CMC discipline was designated as the cross-discipline team lead for NDA 210-089 based on the assessment that MAA safety and efficacy is reliant on product characterization, i.e. particle attributes (size distribution and number) and formulation, and acceptability of a bridge to the listed drug relied upon, Draximage MAA. Other review disciplines would file individual NDA review memos accordingly.

Pharmacology and Toxicology Summary

The mechanism of action for ^{99m}Tc MAA is that radiolabeled particles become mechanically lodged within the terminal precapillary arterioles and capillaries of the lungs following intravenous administration, permitting lung scintigraphic imaging for up to several hours. Entrapped particles are slowly cleared through mechanical fragmentation, induced by changes in pressure and flow in the lungs [1]. 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 [2]. For example, in published studies that evaluated MAA toxicity in dogs, pulmonary distress and increases in pulmonary blood pressure (through occlusion of pulmonary circulation), correlated with the particle size and number of particles injected [1, 3], with greater hemodynamic effects at lower mg doses of MAA as the particle size increased.

The Applicant submitted nonclinical pharmacology and toxicology studies that supported the approval of TechneScan MAA under NDA 017-842. The studies are not adequate to demonstrate safety as they were conducted prior to establishment of GLP and current FDA guidance documents for the conduct of nonclinical studies. No new nonclinical studies were conducted to support approval of the proposed drug product, Pulmotech MAA. However, Pulmotech MAA is of sufficient similarity to the listed drug product Draximage MAA and overall formulation (**Table 1**).

Table 1 Comparison of Proposed Cis Bio US AAI and Draximage MAA Formulations.

Component	Proposed CIS BIO US AAI (Tc-99m MAA)	DraxImage MAA	Comment
Macroaggregated Albumin (MAA)	2 mg	2.5 mg	~ 25% more macroaggregated albumin in DraxImage MAA.
Number of particles per Vial	(b) (4)	Not specified in current labeling, Actual # of particles provided for each batch	(b) (4)
Stannous chloride (b) (4)	≥ 100 µg	60 µg	
Total tin (stannous & stannic chloride)	220 µg	110 µg	
Human serum albumin (HSA)	7.1 mg	5 mg	
(b) (4)			
Sodium chloride	9 mg	1.2 mg	
HCl/NaOH	Adjust pH	Adjust pH	-

The Applicant is therefore relying on a bridge to the listed drug to support reliance on the Agency's finding of safety and effectiveness for DraxImage MAA. The two critical features affecting MAA pharmacodynamics, pharmacokinetics, and toxicology are entirely dependent on MAA product quality through (a) particle size distribution and (b) total number of administered particles. Therefore, nonclinical will rely on the findings from the product quality review team (OPQ) on the Applicant's justification comparing the Draximage MAA and the proposed product, and a thorough evaluation of CMC data demonstrating that any physiochemical differences between Pulmotech MAA and Draximage MAA do not contribute to differences in safety and effectiveness.

In summary, there were no new nonclinical studies submitted by the Applicant to review which would provide additional support of safety for Pulmotech MAA and proposed product labeling information. The safety profile of Technetium Tc 99m MAA is well established based on more than 30 years of clinical experience. This NDA is approvable from a nonclinical perspective pending a determination from CMC regarding the acceptability of the bridge between Pulmotech MAA and the listed drug relied upon, Draximage MAA, and any additional CMC issues.

References

1. Taplin, G.V. and N.S. MacDonald, *Radiochemistry of macroaggregated albumin and newer lung scanning agents.* Semin Nucl Med, 1971. **1**(2): p. 132-52.
2. Lathrop, K.A. and P.V. Harper, *Biologic behavior of 99m Tc from 99m Tc-pertechnetate ion.* Prog Nucl Med, 1972. **1**: p. 145-62.
3. Taplin, G.V., et al., *Lung Photoscans with Macroaggregates of Human Serum Radioalbumin. Experimental Basis and Initial Clinical Trials.* Health Phys, 1964. **10**: p. 1219-27.

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