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APPLICATION NUMBER:

216820Orig1s000

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:	216820
Supporting document/s:	Orig-1; SDN-4
NDA submission date:	30 March 2022
Review completion date:	20 December 2022
Product:	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection
Indication:	Diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. Diagnostic aid in providing renal function, split function, renal angiograms, & renogram curves for whole kidney and renal cortex.
Sponsor:	Jubilant Draximage Inc dba Jubilant Radiopharma (JDI; a.k.a Jubilant)
Clinical Review Division:	Division of Imaging and Radiation Medicine (DIRM)
Pharm/Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM)
Reviewer:	Olayinka A. Dina, D.V.M, Ph.D.
Supervisor/Team Leader:	Jonathan E. Cohen, Ph.D.
Division Director (DIRM):	Libero (Louis) Marzella
Division Director (DPT-RPURM):	Mukesh Summam, PhD, DABT
Project Manager:	Modupe O. Fagbami

Template Version: May 23, 2019

Nonclinical Review

The drug product under evaluation is '*Kit for the Preparation of Technetium Tc 99m Mertiatide'*. Following reconstitution, Technetium Tc 99m Mertiatide will be used as a diagnostic agent to image congenital renal and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients (Jafri et al, 1988; Taylor et al., 1986). As a 505(b)(2) application, NDA 216-820 will rely on previous finding of safety and effectiveness established for the listed drug (LD), Technescan MAG3^{TM} (NDA 019882) manufactured by Curium US LLC (formerly Mallinckrodt, Inc). The suggested dose range employed in the (b) (4) adult patient ((b) (4)) for renal function and imaging studies is 185 MBq to 370 MBq (5 mCi to 10 mCi). In pediatric patients, the recommended dose range is 2.6 MBq/kg to 5.2 MBq/kg (70 µCi/kg to 140 µCi/kg) with a minimum dose of 37 MBq (1 mCi).

Brief Regulatory History:

(b) (4)

The Agency recommended that the kit be submitted as a 505(b)(2) application because the two products do not contain the same inactive ingredients and therefore not Q1/Q2; a 505(b)(2) pathway would also require information to establish a scientific bridge between the proposed drug and the listed drug (LD).There are no other differences between JDI's proposed drug and the LD other than the difference in the hydration status of the stannous chloride (dihydrate for the Applicant's drug and anhydrous for the LD) used in the product formulation (prior to lyophilization), whereas the finished product (lyophilized form) composition is the same as LD where the quantity and hydration state of the stannous chloride are expected to be identical. The Applicant provided justification to establish a scientific bridge between the JDI Mertiatide Kit and the LD, Technescan MAG3^{TM}.

The proposed formulation for *Kit for the Preparation of Technetium Tc 99m Mertiatide* is shown in Table 1 below. (b) (4)
Water for Injection. (b) (4)

Table 1: JDI proposed formulation for Kit for the Preparation of Technetium Tc 99m Mertiatide prior to Lyophilization

Ingredients	Composition		Function	Quality Standard
	Amount per unit (mg/vial)	% w/w		
Active Substance				
Betiatide	1 mg	(b) (4)	(b) (4) (Active Pharmaceutical Ingredient precursor)	Professed
Excipients				
Stannous Chloride Dihydrate	0.2 mg	(b) (4)		NF/Ph.Eur.
Sodium Tartrate Dihydrate	40 mg			NF
Lactose Monohydrate	20 mg			NF/ Ph.Eur /JP
Water for Injection	(b) (4)		(b) (4)	NF/ Ph.Eur /BP

A Brief Summary of Nonclinical studies:

No new nonclinical studies were submitted to the NDA by the Applicant to review. Studies conducted to support the approval of the listed drug under NDA 019-882 included a biodistribution study in rats, acute toxicity studies in mice and rabbits, and subacute toxicity studies in rats and rabbits. There were no mortalities or toxic effects in either species in the acute toxicity study. Tc-99m Mertiatide (Technescan MAG3) was well-tolerated at 1000-fold and 100-fold the maximum clinical dose in mice and rabbits, respectively. In the subacute studies conducted in rats and rabbits, no overt toxic effects were observed. No test article-related pathologic effects were observed in rats and rabbits following 14-day intravenous injection at daily dose levels approximately 10 and 30X the maximum clinical dose, respectively.

Conclusion:

No new nonclinical studies were submitted by the Applicant to review which would provide additional support of safety for "Kit for the Preparation of Technetium Tc 99m Mertiatide Injection" and proposed product labeling information. Overall, the Applicant is relying on a scientific bridge between the proposed drug to the listed drug to support reliance on the Agency's previous findings of safety and effectiveness for Technescan MAG3™ (NDA 019882; CURIUM US LLC). Nonclinical will rely on the findings from the

product quality review team (OPQ) on the Applicant's justification comparing the Technescan MAG3 and the proposed product.

Based on literature (Taylor et al., 2017) administered doses of 99mTc-MAG3 in the range of 300–370 MBq (approximately 8–10 mCi) do not affect the relative function measurements or contribute to interpretation of images in patients suspected of having RVH (right ventricular hypertrophy) or obstruction compared with administration of lower doses. No new safety findings have been reported since the LD was approved in 1990. In summary, this NDA is approvable from a nonclinical perspective pending a determination from CMC regarding the acceptability of the bridge between the technetium Tc 99m mertiatide kit and the LD, Technescan MAG3, and any additional CMC issues.

REFERENCES:

1. Jafri et al (1988).Technetium-99m MAG3, a comparison with iodine-123 and iodine-131 orthoiodohippurate, in patients with renal disorders. J Nucl Med, 29(2):147-58.

2. Taylor et al (1986). Comparison of Iodine-131 OIH and Technetium-99m MAG3 Renal Imaging in Volunteers. J Nucl Med 27:795-803.3. Taylor et al (2017). 99mTc-MAG3: Image Wisely. Radiology, 284(1):200-209.

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/s/

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