APPLICATION NUMBER:

210089Orig1s000

OTHER REVIEW(S)
Divison of Medical Imaging and Radiation Medicine (DMIRM)
Radiation Dosimetry and Dose-Labeling Comments re \(^{99m}\text{Tc-MAA}\)
NDA 210089 and NDA 017881
FDA/CDER/OND/OSM/DMIRM
March 2, 2020

From: Stanley H. Stern, PhD, DMIRM Health Physicist
Through: Anthony Fotenos, MD, PhD, DMIRM Team Leader
Alex Gorovets, MD, DMIRM Deputy Director

To: Qi Feng, MD, PhD, DMIRM Clinical Reviewer
Copy to: Louis Marzella, MD, PhD, DMIRM Director
Janice Weiner, ORP/DRP-I Senior Regulatory Counsel
Alberta E. Davis-Warren, RPM
Thuy M. Nguyen, RPM

Sponsor, NDA 210089: CIS Bio International
Product, NDA 210089: Pulmotech MAA (\(^{99m}\text{Tc-MAA}\))

Sponsor, NDA 017881: Jubilant DraxImage
Product, NDA 017881: DraxImage MAA (\(^{99m}\text{Tc-MAA}\))

Indications (paraphrased):
Technetium Tc 99m Albumin Aggregated Injection (\(^{99m}\text{Tc-MAA}\)) is a radioactive
diagnostic agent which may be used (i) in adult and pediatric patients for lung imaging as
an adjunct in the evaluation of pulmonary perfusion, and (ii) in adults as an imaging
agent to aid in the evaluation of peritoneovenous \(^{(b) (4)}\) shunt patency.

Introduction
The proposed prescribing information [1] of NDA 210089 covering the radiation absorbed-dose
tables and their literature sources is the same as that of the listed drug (NDA 017881) [2, 3]: the
dosimetry is based on literature dated to 1973 – 1980 [cf. notes to refs. 2, 3], and it is not
explicitly sourced to publications of the International Commission on Radiological Protection
(ICRP). To delineate scientific progress since then, we summarize key features of biokinetic and
radiation-transport modeling incorporated into ICRP Publication 128 (2015) [4]. These features
adapt and/or update corresponding aspects of ICRP Publication 53 (1988) [5], and they are
applied in ICRP Publication 128 (2015) [4] to estimate radiation absorbed dose values (per unit
activity administered) for intravenously injected \(^{99m}\text{Tc-labeled Macro-Aggregated Albumin}\)
(MAA).
Conclusion
In view of the scientific and technical advances summarized in the following delineation of biokinetic and radiation-transport modeling of intravenously injected $^{99m}$Tc-MAA for lung-perfusion imaging, in principle *ICRP Publication-128* absorbed-dose values [4] are likely to be more accurate than corresponding values in current $^{99m}$Tc-MAA labeling [2] and proposed product labeling [1]. However, this potential improvement in dosimetric accuracy is unlikely to affect the clinical radiation safety or effectiveness of $^{99m}$Tc-MAA used per current [2] or proposed [1] labeling: large uncertainties in radiation-attributable lifetime cancer-risk projections [26] would likely overwhelm hypothetical improvements that might be expected from updated dosimetry input into risk calculations. In other words, the large uncertainties arising in radiation epidemiological research [27] would likely render quantitative assessment of any putative improvement in the accuracy of cancer-risk evaluation statistically indeterminate as an aspect of radiation safety.

Dosimetry background
Conceptually, according to the internal dosimetry schema of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), average absorbed dose in a particular “target” region is a summation — accounting for all “source” regions — of the arithmetic products of “cumulated activity” in a source region and an associated “S value” [6]. “Cumulated activities” can be estimated from biokinetic modeling of clinical data (or data extrapolated from pre-clinical studies). An “S value” represents the absorbed dose rate (per unit administered activity) incurred from radiant energy transported from a “source” region and imparted to a “target” region. S values are estimated from calculations of Monte Carlo computer simulations of radiation transport in age- and sex-dependent mathematical models of people (“phantoms”) with reference features of body habitus and composition.

Biokinetic modeling of drug uptake, distribution, residence, and excretion can be represented parametrically in several aspects:

(a) Compartmental distribution (i.e., amongst various anatomically associated radioactive-“source” regions),

(b) Biological half-lives (i.e., exclusive of radioactive decay) corresponding to compartmental elimination and/or uptake of the radiopharmaceutical,

(c) Compartmentally respective “time-integrated activity coefficients” which are inclusive of radioactive decay and are commonly referred to as “cumulated activities.”

Biokinetic and radiation-transport modeling in *ICRP Pub 128* and *ICRP Pub 53*
- *ICRP Pub 128* [ref. 4, p. 185, sections C.37.1, C.37.2, and Table C.74]) adapts the same biokinetic model for $^{99m}$Tc-MAA as that used for $^{131}$I-MAA in *ICRP Pub 53* [ref. 5, p. 293], with the modifications that (i) “released technetium is assumed to be excreted by the kidneys according to the model proposed for pertechnetate when a [thyroid] blocking agent has been given” and that (ii) the physical half-life for $^{99m}$Tc is introduced in lieu of that of $^{131}$I in the evaluation of compartmental cumulated activities. *ICRP Pub 53* incorporates the same
adaptation for $^{99m}\text{Tc}$-MAA [ref. 5, p. 223]. Hence, the parameters representing the biokinetic model for $^{99m}\text{Tc}$-MAA in *ICRP Pub 128* [ref. 4, p. 185, Table C.74] have values that are identical (within round-off errors) to those of the biokinetic model for $^{99m}\text{Tc}$-MAA in *ICRP Pub 53* [ref. 5, p. 223]. Adaptation of the biokinetic modeling of $^{131}\text{I}$-MAA [ref. 5, p. 293] to that for $^{99m}\text{Tc}$-MAA means that the $^{99m}\text{Tc}$-MAA modeling is also based on data of the references [14 – 21] (published from 1965 through 1983). These references are listed in *ICRP Pub 53* [ref. 5, p. 293], where the biokinetic modeling is described there as follows:

“Aggregates produced from human serum albumin having a diameter of 10–150 µm, typically around 50 µm, are immediately and completely trapped in the arterioles and capillaries of the lungs after intravenous injection. The elimination of the activity from the lungs is effected in two ways. Most of the activity is released from the aggregate as free iodide...” [modeled as pertechnetate for administered $^{99m}\text{Tc}$-MAA]. “Part of the MAA is broken down to smaller labelled fragments which are transported in the blood to the liver, where they are slowly metabolized with release of the iodine...” [modeled as pertechnetate for administered $^{99m}\text{Tc}$-MAA].

“Quantitative data on the metabolism of iodine- and technetium-labelled MAA in the literature [14 – 21] show a wide variation. Pulmonary clearance is described either as a mono-exponential process with a biological half-time of 1-20 hr, or as a bi-exponential process with half-times of 3.3-6 hr for the dominating rapid phase and about 3 d for the slower phase. Liver uptake is reported in the range of (0–50% and excretion in urine as 20–40% (24 hr) and 42–95% (48 hr).”

“In the model adopted here the activity is assumed to leave the lungs with half-times of 6 hr (0.85) and 3 d (0.15). The liver takes up a fraction of 0.25 with an uptake half-time of 6 hr and an elimination half-time of 5 d. Iodide [pertechnetate] released from the lungs and the liver is excreted by the kidney according to the iodide [pertechnetate] model with blocked thyroid.”

- Whereas the biokinetic parameters associated with $^{99m}\text{Tc}$-MAA injections are identical between *ICRP Pub 128* [ref. 4, p. 185] and *ICRP Pub 53* [ref. 5, p. 223], for some organs the respectively corresponding values of absorbed dose per unit activity administered are different between the two ICRP publications: *cf.* [ref. 4, p. 186] vs. [ref. 5, p. 224]. Contributors to such differences include in *ICRP Pub 128* updated estimates for “S values;” updates in modeling mathematical phantom habitus, organ composition and masses; and updates in modeling biokinetics of sub-systems (e.g., renal transit in kidney-bladder excretion). The following items exemplify the kinds of updates incorporated into *ICRP Pub 128* (2015) since the 1988 publication of *ICRP Pub 53*:
  - “The masses of the organs and tissues are inherent in the S values used...[7, 8]. The masses of the phantoms used for calculation of the S values are those presented by Stabin and Siegel (2003) [7] (Table A.1).” [See ref. 4, p. 39, paragraph (A1).]
  - “An age-related bladder voiding model is used. The voiding periods are based on urinary production rates as described in *Publication 89* (ICRP, 2002) [9], and volume of the content as described by Stabin and Siegel (2003) [4]. The voiding periods [2.0, 3.0, and 3.5 h] are presented in Table A.4.” [See ref. 4, p. 45, paragraph (A15).]
  - “For the present report [4], the calculations [of mean absorbed dose to bone surfaces and red marrow] are based on S values derived by Stabin and Siegel (2003) [7], based on methods for calculating the absorbed fraction for the non-penetrating radiation developed by Eckerman and Stabin (2000) [10] and Bouchet et al. (2000) [11].” [See ref. 4, p. 46, paragraph (A21).]
For substances actively taken up in the salivary glands, “an approximate absorbed dose...is estimated...using the unit density sphere model [for S-value source-region self-irradiation] in the...MIRDOSE3 program (Stabin, 1996) [12]. The S values have been calculated considering the three pairs of salivary glands (parotid, submaxillary, and sublingual) with masses according to *Publication 23* (ICRP, 1975) [13]. Those masses do not deviate significantly from those reported in the updated version, *Publication 89* (ICRP, 2002) [9]. To estimate the absorbed dose from source in other organs, the brain is used as a substitute target organ, except in cases when the brain is also a source.” [See ref. 4, p. 50, paragraph (A35).]

• References [14 – 21], which are applied as a basis for biokinetic modeling, do not indicate that any of the subjects in the associated clinical studies were pediatric patients. We therefore assume that the same biokinetic model was applied to the pediatric and to the adult mathematical phantoms for calculation of radiation absorbed-dose estimates in *ICRP Pub 53* [5] and in *ICRP Pub 128* [4] for $^{99mTc}$MAA. However, the biodistribution and cumulated activities of a radioisotope in source regions are likely age dependent since the masses, shapes, atomic compositions, and vasculature of tissue are age dependent. For example, ref. [22] states:

“In the human infant the alveoli increase in number rapidly during the first year, and then more gradually, reaching adult levels at about 8 years of age” [23]. “Similarly there is an increase in the number of small pulmonary arteries, particularly between the ages of 4 mo and 3 yr” [24]. “While the precise age at which alveolar multiplication ceases is not certain, one estimate showed a rapid increase from about 1/10 to 1/3 of adult values during the first year of life and to ½ the adult number by 3 yr” [25].

As neither biokinetic modeling, nor pediatric phantoms, nor S-values reflect the post-natal growth and development of lung alveoli and pulmonary arteries [cf. ref. 7 and references cited therein], estimates of absorbed-dose values for ages $< 10$ years-old are likely to be relatively more inaccurate than those for ages $\geq 10$ years-old.

**References and notes**


**Note:** Footnotes 1 and 2 to Table 5 (“Pediatric Radiation Dose from Tc 99m MAA for Lung Imaging”) refer to

1.  “Kaul et al., Berlin 1973” and to  
2.  “For the newborn, 1-year old, and 5-year old, ‘S’ values calculated from the preliminary phantoms of ORNL...” For the “10-year old, 15-year old and adult ‘S’ values were taken from Henrichs et al., Berlin, 1980.”

In this label there is no further detailed specification of the references to “Kaul et al.,” “Henrichs et al.,” or the ORNL preliminary phantoms. The following reference [3], however, includes complete citations for the “Kaul et al.” and “Henrichs et al.” references.

Note: Footnotes 1 and 2 to Table 5 (“Paediatric Radiation Dose from Tc-99m MAA for Lung Imaging”), referring to “Kaul et al., Berlin 1973” and to “Henrichs et al., Berlin, 1980” are cited as follows in the reference list of this label. We conjecture that the first citation which follows is probably associated with the book and abstract hyperlinked to the following web page: https://www.osti.gov/etdeweb/biblio/7245553.


Note: Section C.37 (pp. 185-186 of Publication 128) covers $^{99m}$Tc-labelled MAA, and Table C.75 (p. 186) presents estimates of radiation absorbed dose per unit activity. Also, the reference in ICRP Publication 128 (p. 185) to ICRP Publication 53 includes an incorrect publication date for Publication 53 due to a printing error in the original Publication 53. The correct publication date for ICRP Publication 53 is 1988, as stated (and previously confirmed) as follows in citation [5].


This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STANLEY H STERN
03/20/2020 11:40:13 AM

ANTHONY F FOTENOS
03/20/2020 12:02:52 PM

ALEXANDER GOROVETS
03/20/2020 12:04:11 PM
1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 13, 2020 for Pulmotech MAA. We reviewed the revised container label and carton labeling for Pulmotech MAA (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.\(^a\)

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

\(^a\) Vee S. Label and Labeling Review for Pulmotech MAA (NDA 210089). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 16. RCM No.: 2019-1296.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH K VEE
03/16/2020 12:38:49 PM

HINA S MEHTA
03/19/2020 01:19:17 PM
MEMORANDUM

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, M.D., Pediatric Team Leader
John J. Alexander, M.D., M.P.H., Deputy Director,
DPMH, ODE IV, OND

To: Division of Medical Imaging and Radiation Medicine (DMIRM)

Drug: Pulmotech MAA (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection)

Application Number: NDA 210089 (IND 132108)

Applicant: Cis Bio International

Proposed Indication: • As a 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 peritoneovenous (LeVeen) shunt patency.

Proposed Dosage Form: Lyophilized powder containing 2 mg Albumin Aggregated in a 15 mL multi-dose vial for preparation with Sodium Pertechnetate Tc 99m

Route of Administration: For intravenous and intraperitoneal use
Proposed Dosing Regimen:

- The recommended intravenous dose range for the average (70 kg) Adult patient for lung imaging is 37 to 148 MBq (1 to 4 mCi).
- The suggested 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).
- 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).
- The recommended number of particles per single injection is 200,000 to 700,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 to 1.9 mL.

Consult Request: DMIRM engaged the DPMH-Pediatrics Team on July 8, 2019 to provide assistance with labeling recommendations for pediatric use that comply with the Physician Labeling Rule format.

Materials Reviewed:

- DPMH consult request (dated July 8, 2019 in DARRTS under NDA 210089)
- Current Draximage (Technetium Tc 99m Albumin Aggregated Injection), NDA 017881 labeling (October 31, 2017 in FDALabel)
- Applicant’s proposed labeling for NDA 210089 (submitted on June 11, 2019)
- Minutes for Type B Pre-NDA Meeting for IND 132108 on May 3, 2017 (dated May 31, 2017 in DARRTS)
- Acknowledge Withdrawal of Approved NDA Letter, NDA 017842 (dated November 25, 2008)
- Withdrawn FR Notice Effective Letter, NDA 017842 (dated August 19, 2008)

I. Regulatory History of this Application

Cis Bio International submitted a 505(b)(2) new drug application (NDA) seeking approval for Pulmotech MAA (technetium Tc 99m albumin aggregated) Injection for the following two proposed indications: (1) use as a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients and (2) may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (LeVeen) shunt patency. Pulmotech MAA is composed of aggregated human albumin labeled with the 99mTc radioisotope.
Prior to 2009, Mallinckrodt Nuclear Medicine LLC, marketed Technetium Tc99m albumin aggregated under NDA 017842 Technescan MAA. On July 24, 2008, Mallinckrodt submitted a request to withdraw NDA 017842, Technescan MAA, because it had stopped marketing the product. FDA published a notice in the Federal Register on May 19, 2009, withdrawing approval of the application, effective June 18, 2009.1

The applicant, Cis Bio International, is proposing to introduce a kit for the preparation of technetium Tc 99m aggregated albumin into the US marketplace. The applicant submitted this NDA through the 505(b)(2) pathway that relies upon FDA’s finding of safety and effectiveness for Draximage MAA (NDA 017881) as the listed drug to support approval of the proposed product. The application does not propose a new active ingredient, new indications, new route of administration, new dosage form or new dosing regimen for adult and pediatric patients and therefore, includes no triggers to the Pediatric Research Equity Act.

II. DPMH Review of Pediatric Use Labeling:

This DPMH labeling review will focus on edits to Section 2 (Dosing and Administration) and Subsection 8.4 (Pediatric Use). DPMH proposes the following recommendations based on labeling discussions between DMIRM and DPMH in which underlined text represents proposed additions and strikethroughs in the relevant text represent proposed deletions.

Application Holder’s Proposed Labeling:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

Pediatric Patients

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 per kilogram (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 MBq to 18.5 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 will vary with age and weight patient as indicated in Table 1.

**Table 1 – Pediatric**

<table>
<thead>
<tr>
<th>Age</th>
<th>Newborn</th>
<th>1 year</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>3.5</td>
<td>12.1</td>
<td>20.3</td>
<td>33.5</td>
<td>55</td>
</tr>
<tr>
<td>Max. recommended dose</td>
<td>MBq</td>
<td>mCi</td>
<td>MBq</td>
<td>mCi</td>
<td>MBq</td>
</tr>
<tr>
<td>18.5</td>
<td>0.5</td>
<td>22.2</td>
<td>0.6</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>Range of particles administered</td>
<td>10,000 to 50,000 to 200,000 to 200,000 to 700,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorbed dose</td>
<td>mGy</td>
<td>rad</td>
<td>mGy</td>
<td>rad</td>
<td>mGy</td>
</tr>
<tr>
<td>Total body</td>
<td>0.6</td>
<td>0.06</td>
<td>0.3</td>
<td>0.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Lungs</td>
<td>19</td>
<td>1.9</td>
<td>6.6</td>
<td>0.66</td>
<td>5.8</td>
</tr>
<tr>
<td>Liver</td>
<td>1.4</td>
<td>0.14</td>
<td>0.6</td>
<td>0.06</td>
<td>0.62</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>2.1</td>
<td>0.21(1)</td>
<td>1.5</td>
<td>0.15(1)</td>
<td>3.1</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.38</td>
<td>0.038</td>
<td>0.2</td>
<td>0.02</td>
<td>0.19</td>
</tr>
<tr>
<td>Testes</td>
<td>0.31</td>
<td>0.031</td>
<td>0.13</td>
<td>0.013</td>
<td>0.19</td>
</tr>
</tbody>
</table>

(1) 2 hour voiding interval
(2) 4.8 hour voiding interval

**Adults and Pediatric Patients**

Visually inspect for particulate matter and discoloration prior to administration.

Measure by a suitable radioactivity calibration system immediately prior to administration. Mix the contents of the vial by gentle inversion just prior to withdrawing a patient dose.

Mix the contents of the syringe just before injection. If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation. For optimal results and because of rapid lung clearance of the radiopharmaceutical, position the patient under the imaging apparatus before administration. Slow injection is recommended. Lung imaging may begin immediately after intravenous injection of the radiopharmaceutical. Due to high kidney uptake, imaging later than one-half hour after administration will yield poor results.
2.2 Radiation Dosimetry

Adult Patients

The estimated absorbed radiation doses\(^3\) to an average ADULT adult patient (70 kg) from an intravenous injection of 148 MBq (4 mCi) of Technetium Tc 99m Albumin Aggregated Injection are shown in Table 2.

Table 2 – Absorbed Radiation Doses

<table>
<thead>
<tr>
<th>Organs</th>
<th>mGy/148 MBq</th>
<th>rad/4 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>0.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Lungs</td>
<td>8.8</td>
<td>0.88</td>
</tr>
<tr>
<td>Liver</td>
<td>0.72</td>
<td>0.072</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.68</td>
<td>0.068</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.44</td>
<td>0.044</td>
</tr>
<tr>
<td>Bladder Wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr. void</td>
<td>1.2</td>
<td>0.12</td>
</tr>
<tr>
<td>4.8 hr. void</td>
<td>2.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Testes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr. void</td>
<td>0.24</td>
<td>0.024</td>
</tr>
<tr>
<td>4.8 hr. void</td>
<td>0.26</td>
<td>0.026</td>
</tr>
<tr>
<td>Ovaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr. void</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>4.8 hr. void</td>
<td>0.34</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*Assumptions: Calculations for the absorbed radiation dose are based upon an effective half-time of 3 hours for the open shunt and a physical half-life of 6 hours for the closed shunt and**
an even distribution of the radiopharmaceutical in the peritoneal cavity with no biological clearance.

**Pediatric Patients**

In pediatric patients, the radiation absorbed doses using the maximum recommended dose for lung imaging are based on 1.85 MBq (50 μCi) per kilogram of body weight (except in the neonates where the maximum recommended dose of 18.5 MBq (500 μCi) is used) and are shown in Table 1.

**Reviewer Comment:** DPMH recommended clarifying the adult versus the pediatric dosing and administration instructions by creating headings for adults and pediatric patients in sections 2.1 and 2.2 and organizing the relevant language under those headings. Otherwise, DMIRM made the specific edits to the content of sections 2.1 and 2.2 with regards to wording; however, DMIRM’s edits appear reasonable. Of note, no specific pediatric age range has been specified because the product is proposed for use for the entire pediatric population for lung imaging.

## 8 USE IN SPECIFIC POPULATIONS

### 8.4 Pediatric Use

Technetium Tc 99m Albumin Aggregated Injection is indicated for lung scintigraphy as an adjunct in the evaluation of pulmonary perfusion in pediatric patients [see Dosage and Administration (2)]. The safety profile of Technetium Tc99m Albumin Aggregated Injection is similar to the one in adults.

**Reviewer comment:** In accordance with the March 2019 Pediatric Labeling Guidance, this section should include a pediatric use statement or reasonable alternative statement when a drug is approved in pediatric patients. The FDA may permit use of alternative statements in the Pediatric Use subsection if it determines that none of the other use statements suggested in the guidance describing the determination of safety and effectiveness are appropriate or relevant to the drug’s labeling. The data supporting the Draximage approval is not outlined in its respective labeling and unavailable for this 505(b)(2) application to reference. Therefore, we recommend
avoiding a description of the basis for approval and simply noting that this product is indicated for use in the pediatric population for lung imaging and including a cross-reference to the Dosing and Administration section which provide more detailed information about recommended use of this proposed product in the pediatric population. Additionally, DMIRM determined that literature data show a similar safety profile in pediatric patients and adults, which will be described in this subsection. DPMH initially recommended a statement to convey that the product is not indicated for evaluation of peritoneovenous shunt patency in pediatric patients. However, DMIRM did not agree with this proposal. DMIRM expressed the expectation that the drug could be used for evaluation of shunt patency in pediatric patients and did not want to include language in this subsection that potentially limits access. Therefore, while the Indications and Usage section will clearly state that the populations for which each indication is approved, Subsection 8.4 will simply describe that this product is indicated for lung scintigraphy as an adjunct in the evaluation of pulmonary perfusion in pediatric patients.

Consistent with Draximage labeling, the applicant proposed labeling in the Warnings and Precautions section for this product to state that , in addition to text in the Pediatric Use Subsection that is based on this warning. DPMH initially made edits to this language to clarify the populations to which this warning relates based on the applicant’s proposed Warning and Precautions and discussion with DMIRM. However, DMIRM subsequently reviewed this warning information and determined that studies have not confirmed the potential risk noted in Draximage labeling of . Therefore, they decided to remove this language from the Warnings and Precautions section and consequently, proposed removing the related language from Subsection 8.4 as well.

III. DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant’s draft labeling. DPMH provided recommended labeling for the pediatric population based on labeling discussions between DMIRM and DPMH and in accordance with 21 CFR 201.57(c)(9)(iv). DPMH’s input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the application holder and may not fully reflect changes suggested here.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONA K KHURANA
03/16/2020 12:56:03 PM
Memorandum

Date: March 9, 2020

To: Qi Feng, M.D.
Division of Medical Imaging Products (DMIP)

Thuy Nguyen, Regulatory Project Manager, DMIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for PULMOTEC MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection), for intravenous and intraperitoneal use

NDA: 210089

In response to DMIP’s consult request dated June 24, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for PULMOTEC MAA.

PI: OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on February 4, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 13, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID F FOSS
03/09/2020 12:45:36 PM
DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs, ODE-IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD  20993  
Telephone  301-796-2200  
FAX  301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:  July 8, 2019
From:  Jane Liedtka M.D., Medical Officer (MO), Maternal Health Team, Division of Pediatric and Maternal Health (DPMH)
Through:  Miriam Dinatale, DO, Team Leader, Maternal Health Team, DPMH  
Lynne P. Yao, MD, Director, DPMH
To:  Qi Feng MD, MO  
Division of Medical Imaging Products (DMIP)
NDA Number:  210089
Drug:  Pulmotech MAA (Technetium Tc 99m Albumin Aggregated) Injection
Applicant:  Cis Bio International
Indication:  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.

DMIP submitted a consult request to DPMH on July 8, 2019 to assist with PLLR labeling. DPMH participated in a labeling meeting with DMIP on January 8, 2020 and proposed labeling recommendations for the above referenced NDA. These were updated and included recommendations for interruption of breastfeeding based on the Nuclear Regulatory Commission Guidelines.

DPMH- Maternal Health, has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Jane Liedtka, MD  
DPMH Maternal Health Team Leader- Miriam Dinatale, DO

Reference ID: 4629566
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Gettie Audain
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANE E LIEDTKA
03/09/2020 04:17:27 PM

MIRIAM C DINATALE
03/09/2020 04:29:03 PM

LYNNE P YAO
03/09/2020 05:00:27 PM
**LABEL AND LABELING REVIEW**
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

<table>
<thead>
<tr>
<th><strong>Date of This Review:</strong></th>
<th>December 16, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requesting Office or Division:</strong></td>
<td>Division of Medical Imaging Products (DMIP)</td>
</tr>
<tr>
<td><strong>Application Type and Number:</strong></td>
<td>NDA 210089</td>
</tr>
<tr>
<td><strong>Product Name and Strength:</strong></td>
<td>Pulmotech MAA (kit for the preparation of technetium 99m albumin aggregated injection) for injectable suspension, 2 mg per vial (albumin aggregated)</td>
</tr>
<tr>
<td><strong>Product Type:</strong></td>
<td>Single Ingredient Product</td>
</tr>
<tr>
<td><strong>Rx or OTC:</strong></td>
<td>Prescription (Rx)</td>
</tr>
<tr>
<td><strong>Applicant/Sponsor Name:</strong></td>
<td>Cis Bio International</td>
</tr>
<tr>
<td><strong>FDA Received Date:</strong></td>
<td>June 11, 2019 and September 13, 2019</td>
</tr>
<tr>
<td><strong>OSE RCM #:</strong></td>
<td>2019-1296</td>
</tr>
<tr>
<td><strong>DMEPA Safety Evaluator:</strong></td>
<td>Sarah K. Vee, PharmD</td>
</tr>
<tr>
<td><strong>DMEPA Team Leader:</strong></td>
<td>Hina Mehta, PharmD</td>
</tr>
</tbody>
</table>
1 REASON FOR REVIEW

Cis Bio submitted a 505(b)(2) NDA for kit for the preparation of technetium Tc 99m albumin aggregated injection (NDA 210089). We reviewed the proposed prescribing information (PI), container label, and carton labeling for areas of vulnerability from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>N/A</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>N/A</td>
</tr>
<tr>
<td>ISMP Newsletters*</td>
<td>N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>B</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, carton labeling, container label, radioassay label, and lead shield labeling for Pulmotech MAA for areas of vulnerability that may lead to medication errors. Our review of the proposed labeling identified several areas that can be improved to increase the prominence of important information.

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We conclude that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for Cis Bio International to address our concerns. We advise that these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information
1. To increase readability, a unit-of-measure should follow each numeric dose designation. Include, 'MBq', 'mcCi' and 'mCi' after each numeric value pertaining to dosage and administration throughout the PI.

2. To increase readability and reduce clutter, use abbreviations for units of measure where appropriate (replace megabecquerels with MBq, etc.)

3. Dangerous abbreviations, symbols, and dose designations that are included in Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols and Dose Designations appear in the Highlights and Dosage and Administration sections of the PI. As part of a national campaign to avoid the use of dangerous dose designations, FDA agreed not to approve such error dose designations in the approved labeling of products. Thus, replace “μ” for micro with “mc” (e.g. revise 50 μCi/kg to 50 mcCi).

B. Highlights of Prescribing Information

1. Dosage and Administration
   a. Revise the first bullet to “For lung in adults, recommended dose is 37 MBq to 148 MBq (1 mCi to 4 mCi) intravenously (2.1)” for clarity.
   b. Revise the second bullet to “For peritoneovenous shunt in adults, recommended dose is 37 MBq to 111 MBq (1 mCi to 3 mCi) (2.1)” for clarity.
   c. Revise the third bullet to “For lung in pediatrics recommended dose is 0.925 MBq/kg to 1.85 MBq/kg (25 mcCi/kg to 50 mcCi/kg) intravenously (2.1)” for clarity.
   d. The dosage for newborns is not clearly defined. We recommend clarification on age of newborn and clarification if dosage is based on weight.
   e. We recommend revising the last bullet to read “See full prescribing information for preparation, administration, imaging, and radiation dosimetry information (2.2, 2.3).”.

C. Full Prescribing Information

1. Section 2, Dosage and Administration
   a. We recommend removing the reference to as this information is not needed.

2. Section 16, How Supplied/Storage and Handling
   a. Remove reference to as this information is not needed.
   b. Consider revising the kit components as follow for readability:
Pulmotech MAA kit is available as:

- Carton of 5 vials with 1 prescribing information and 5 radioassay information labels (NDC 69945-139-20).
- Carton of 30 vials with 1 prescribing information and 30 radioassay information labels (NDC 69945-139-40).

4.2 RECOMMENDATIONS FOR CIS BIO INTERNATIONAL

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)

1. The route of administration, "For Intravenous Use Only" is currently embedded among other information and therefore may be easily missed. Please move to directly below the product strength and bold to make it more prominent.

2. Decrease the prominence of the statement "Rx Only" by debolding as this information appears more prominent than the rest of the information on the principal display panel.

3. To increase readability, a unit-of-measure should follow each numeric dose designation. Include, 'MBq', 'mcCi' and 'mCi' after each numeric value pertaining to strength and dosage throughout.

   a. To increase readability and reduce clutter, use abbreviations for units of measure where appropriate (replace megabecquerels with MBq, etc.)

B. 5 Vial Kit Labeling

1. Revise the statement "Dosage: See prescribing information" per 21 CFR 201.55.

2. Remove the "…." statement as dosage is variable.

3. Under “Kit Contains” revise "(b) (4)" to read “1 Prescribing Information”.

4. Consider reorienting the linear barcode to a vertical position so that the barcode can be scanned properly. Barcodes placed in a horizontal position may not scan due to vial curvature.a

5. The net quantity and package type are currently missing on the principal display panel (PDP) per 21 CFR 201.51. (See also Draft Guidance: Container and Carton, April 2013 (lines 731-733, 764-766)). Include the net quantity of “5 single-dose vials” on the PDP.

---

C. 30 Vial Carton Labeling

1. Revise the statement “Dosage: See prescribing information” per 21 CFR 201.55.

2. Remove the “Dosage: See prescribing Information” statement as dosage is variable.

3. Under “Carton Contains” revise “Dosage: See prescribing Information” to read “1 Prescribing Information”.

4. The net quantity and package type are currently missing on the principal display panel (PDP) per 21 CFR 201.51 (See also Draft Guidance: Container and Carton, April 2013 (lines 731-733, 764-766)). Include the net quantity of “5 single-dose vials” on the PDP.

5. The location of the Lot and Expiration date is currently missing. Please include including the Lot and Expiration date on the carton.

D. Container (Vial) label

1. The container label for the vial does not have an NDC number. Please consider placing the NDC number on the vial label. The vial label should contain the NDC number with the package code (i.e., the last 2 digits) assigned to the vial presentation which should be different from the package codes for the cartons containing 5 and 30 vials respectively.

2. Revise the recommended dosage statement to “Dosage: See prescribing information” as dose is variable and per 21 CFR 201.55.

E. Radio Assay Label

1. Revise the “Discard after__/__/__” to “Discard after__/__/__”. We recommend, “Discard after__/__/__” since “Discard after” is an affirmative statement and has been shown to result in the desired action. Additionally, the “__/__/__” statement will alert the healthcare provider to write a complete date (month, day, and year) on the container label.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pulmotech MAA received on September 13, 2019 from Cis Bio International, and the listed drug (LD).

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Pulmotech MAA and the Listed Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Name</strong></td>
</tr>
<tr>
<td>Initial Approval Date</td>
</tr>
<tr>
<td>Active Ingredient</td>
</tr>
</tbody>
</table>
| Indication | Technetium Tc 99m Albumin Aggregated Injection is a radioactive diagnostic agent indicated for:  
- (b) (4) lung as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.  
- (b) (4) in the evaluation of peritoneovenous shunt patency. | 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 (LeVeen) shunt patency. |
| Route of Administration | Intravenous and intraperitoneal injection | |
| Dosage Form | for injectable suspension | |
| Strength | 2 mg per vial (albumin aggregated) | 2.5 mg per vial (albumin aggregated) |
| Dose and Frequency | The recommended intravenous dose range for the average (70 kg) ADULT patient for lung imaging is 37 to 148 megabecquerels (1 to 4 millicuries) of Technetium Tc 99m Albumin Aggregated Injection after preparation with oxidant-free Sodium | The recommended intravenous dose range for the average (70 kg) ADULT patient for lung imaging is 37 to 148 megabecquerels (1 to 4 millicuries) of Technetium Tc 99m Albumin Aggregated Injection after reconstitution with oxidant-free Sodium |

Pertechnetate Tc 99m Injection.

The suggested intraperitoneal dosage range for peritoneovenous shunt patency evaluation is 37 to 111 megabecquerels (1 to 3 millicuries).

The suggested intraperitoneal dosage range used in the average patient (70 kg) for peritoneovenous (LeVeen) shunt patency evaluation is 37 to 111 megabecquerels (1 to 3 millicuries).

The suggested percutaneous transtubal (efferen limb) dosage range for the average patient (70 kg) is 12 to 37 megabecquerels (0.3 to 1 millicurie) in a volume not to exceed 0.5 mL.

In PEDIATRIC patients, the suggested intravenous dose to be employed 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; a usual dose is 1.11 MBq per kilogram (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 to 18.5 MBq (200 to 500 μCi).

The recommended number of particles per single injection is 200,000 to 700,000 with the suggested number being 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 to 1.9 mL.

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>(b) kit five (5) vials (NDC# 69945-139-20)</th>
<th>Pertechnetate Tc 99m Injection.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 multi-dose glass vials. Each vial contains a non-radioactive</td>
<td></td>
</tr>
<tr>
<td>or a carton of thirty (30) vials (NDC# 69945-139-40).</td>
<td>sterile, nonpyrogenic lyophilized mixture of: 2.5 mg of albumin aggregated, 5 mg of human serum albumin, 0.06 mg (minimum) of stannous chloride (maximum stannous and stannic chloride 0.11 mg), and 1.2 mg of sodium chloride; 30 Radiation Labels; 1 Package Insert.</td>
<td></td>
</tr>
<tr>
<td>each five (5) vial kit one (1) and five (5) radioassay information labels.</td>
<td>and thirty (30) radioassay information labels.</td>
<td></td>
</tr>
<tr>
<td>thirty (30) vial carton one (1)</td>
<td>Storage</td>
<td></td>
</tr>
<tr>
<td>and thirty (30) radioassay information labels.</td>
<td>The reaction vial contains no bacteriostatic preservative. Store the unreconstituted reaction vials at 2 to 25 °C (36 to 77 °F). After labeling with technetium Tc-99m, store the reconstituted product at 2 to 8 °C (36 to 46 °F) when not in use and discard within 12 hours (See Directions For Preparation).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Storage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>stored at 2° to 25°C (36° to 77°F) before preparation.</td>
<td></td>
</tr>
<tr>
<td>after preparation, at 2° to 8°C (36° to 46°F).</td>
<td></td>
</tr>
</tbody>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Pulmotech MAA labels and labeling submitted by Cis Bio International.

- Container label received on September 13, 2019
- Carton labeling received on September 13, 2019
- Prescribing Information (Image not shown) received on September 13, 2019

B.2 Label and Labeling Images

---

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH K VEE
12/16/2019 10:50:47 AM

HINA S MEHTA
12/17/2019 02:36:20 PM