CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022335Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	022335
PDUFA Goal Date	Sept 29, 2023
OSE RCM #	2023-4310
Reviewer Name(s)	Somya Dunn, MD
Acting Team Leader	Timothy Bernheimer, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	Sept 26, 2023
Established Name	Tc 99m carbon inhalation aerosol
Trade Name	Technegas
Name of Applicant	Cyclomedica Australia Pty Ltd.
Therapeutic Class	Radioactive Diagnostic Agent
Dosing Regimen	• (b) (4) • For adults, the target administered dose is achieved at an imaging count rate of 1,500 to 2,500 per second. • For pediatric patients, the target administered dose is achieved at an imaging count rate of 500 to 1,000 per second.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Technegas (Tc 99m carbon inhalation) is necessary to ensure the benefits outweigh its risks. Cyclomedica Australia Pty Ltd. (the Applicant) submitted a New Drug Application (NDA) 022335 for Technegas with the proposed indication for lung ventilation imaging in adults and pediatric patients 6 years of age and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging.

The clinical review team recommends approval of Technegas on the basis of the efficacy and safety information currently available. The Prescribing Information (PI) will contain a *Warnings and Precautions* for the risk of decreased oxygen saturation as well as radiation exposure risk. For most patients the use of room air after the first breath generally resolves the transient hypoxia or resolution occurs with supplemental oxygen. The radiation exposure risk is a class risk. The procedure would be under the supervision of diagnostic nuclear radiologists or nuclear medicine physicians. They, and the healthcare staff working in the facility, should be knowledgeable about safe handling procedures and protecting patients and be aware of the risk of decreased oxygen saturation and have proper interventions on site, in this case supplemental oxygen.

DRM has determined that a REMS is not necessary to ensure the benefits of Technegas outweigh the risks. The risk can be conveyed through the PI and appropriately managed by the healthcare providers.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for Tc 99m carbon inhalation aerosol (Technegas) New Drug Application (NDA) 022335 to ensure the benefits outweigh the risks. Cyclomedica Australia Pty Ltd (hereafter referred to as the Applicant) submitted NDA 022335 with a proposed indication for use in adults and pediatric patients 6 years of age and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging.

This application is under review in the Division of Imaging and Radiological Medicine (DIRM). The Applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tc 99m carbon inhalation aerosol (Technegas) is technetium-99m labeled carbon designed as a radioactive diagnostic imaging agent. The Applicant's proposed indication is for use in adults and pediatric patients 6 years of age and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging. Technegas distributes to areas of the lungs that are ventilated, where it can then be imaged and visualized using a gamma camera. The areas that are visualized correspond to ventilated lung segments.

Technegas is prepared at the point of use by the TechnegasPlus system and is delivered to patients using a separate Patient Administration Set (PAS) which is to be disposed of as radioactive waste after each patient use.

The proposed kit for the preparation of Technegas includes a 1.25 gram black to dark grey oval shaped graphite carbon crucible (Technegas Crucible). Upon addition of sodium pertechnetate Tc 99m injection to the Technegas Crucible, the Technegas Plus system will provide Technegas Aerosol for oral inhalation. For ventilation/perfusion (V/Q) imaging, Technegas distributes into the bronchoalveolar regions and remains in place sufficiently long to collect multiple views of the lungs enabling comparison to the perfusion images.

Technegas is a ventilation imaging agent marketed in 59 countries worldwide. It was first approved in Australia in 1987 and, as of the end of 2019, Technegas is estimated to have been administered a total of 3.9 million times. Technegas is not considered a new molecular entity.[a] The product Tc99m has already been approved in NDA 017243 as an intravenous diagnostic radiopharmaceutical for several types of imaging including the thyroid and bladder.

If approved, Technegas will be given to patients for evaluation of PE in hospitals and nuclear medicine practices. It will generally be administered by nuclear medicine technologists under the supervision of diagnostic nuclear radiologists or nuclear medicine physicians in facilities where gamma and/or Single-photon emission computed tomography (SPECT) cameras housed.[b] Other gases used for this indication are also radioactive.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 022335 relevant to this review, for more details see the FDA BLA/NDA 022335 Multi-Disciplinary Review:

- 12/15/2008: The Applicant submitted a 505(b)(2) NDA 022335.
- 2/17/2009: The Applicant withdrew the NDA prior to its filing date
- 3/26/2020: NDA 022335 was resubmitted
- 6/25/ 2021: A CRL was sent to the Applicant, Cyclomedica.
- 7/29/2022: FDA granted Cyclomedica's request for an extension to respond to the CRL until January 31, 2023.
- 1/4/2023: FDA granted a further extension due to the global shortage of Molybdenum 99m (Mo99), the precursor to Sodium Pertechnetate Tc99m, the isotope used to manufacture Technegas.
- 3/29/2023: Cyclomedica re-submitted the NDA

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

A pulmonary embolism (PE) is an arterial blockage in the lungs that commonly results from venous thromboembolism. In most cases, the thromboembolism travels to the lungs from veins of the lower extremities. Patients can present in a range of clinical states from shock or sustained hypotension to mild dyspnea. In some cases, PE can be asymptomatic and identified incidentally when patients are imaged for other purposes.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

The incidence of PE is estimated to be approximately 60 to 70 per 100,000.[1 c] PE is very serious condition and can result in sudden death or cause morbidity or mortality through chronic thromboembolism induced pulmonary hypertension. If untreated, acute PE is associated with a significant mortality rate (as high as 30%), whereas the death rate of diagnosed and treated PE is 8%.[1,d] Up to 10% of acute PE patients die suddenly. Anticoagulation therapy is the treatment for PE. Due to the dynamic changing pattern of perfusion in PE, imaging for PE diagnosis should be carried out as soon as the condition is suspected, optimally within 24 hours after onset of symptoms.[2] Pulmonary ventilation imaging is combined with pulmonary perfusion imaging to generate the V/Q scan.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Diagnoses of PE consists of a sequential workup including a clinical assessment, d-dimer testing, and multidetector computed tomography (MDCT) or V/Q scanning. Computed tomography pulmonary angiography (CTPA) and V/Q imaging are the principal imaging modalities for diagnosing PE. CTPA requires intravenously injected iodinated contrast. CTPA associated risks include radiation exposure and adverse reactions caused by the concomitant use of iodinated contrast.

As shown in Table 1, drugs approved for pulmonary ventilation studies include the inert gases Kr-81m, Xenon-133 and the aerosol 99mTc-diethylenetriaminepentaacetate (DTPA). Kr-81m has been withdrawn from the market for commercial reasons. The acquisition time for Xe-133 is limited and therefore the imaging views are limited. DTPA aerosol administration requires a closed nebulizer and the product has the propensity to deposit in central airways that experience turbulent airflow.[2]

Table 1 Radiopharmaceuticals Approved for Ventilation Scans

Product Name	Approval Date	Indication	Status
Xenon Xe 133 gas	10/10/1974	for the evaluation of pulmonary function and for imaging the lungs	On the market
Krypton Kr-81m Gas	06/12/1980	pulmonary ventilation studies to assess and evaluate regional pulmonary function in lung diseases	Withdrawn on 04/26/2001 (not for safety reasons)
DRAXIMAGE DTPA Tc99m pentetate	12/26/2017	lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging in adult and pediatric patients.	On the market

Source: Table 1 FDA NDA/BLA 021164 Multi-Disciplinary Review for March 26, 2020 submission, DARRTS June 25, 2021.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug*

4 Benefit Assessment

The Applicant's Phase 3 study CYC-009 was the primary study submitted to support efficacy for Technegas. Study CYC-009 was adequate and well controlled and supported the indication of Technegas as a radioactive diagnostic imaging agent for lung ventilation scintigraphy in adult and pediatric patients to evaluate pulmonary function. CYC-009 included multiple independent imaging readers as well as pre-specified success criteria. A second study CYC-008 provided confirmatory evidence of effectiveness and supported the indication of Technegas for evaluation of PE, when paired with perfusion imaging.

The data from CYC-009 suggests that Technegas is similar to Xenon-133 with respect to pulmonary ventilation distribution imaging all lung regions (these are divided into six parts) using a three-point ventilation score. Each blinded reader's scores were analyzed and there was an overall agreement with 97.18% confidence interval (CI). Mathematical computation results are presented in the Table 2. The review team was able to verify the Applicant's computations and agreed with these findings.

Table 2 Generalized Estimating Equation (GEE) Estimates of Percent Agreement Between Xe-133 Scores and Technegas Scores - FAS Population

Reader ID Paired Image Sets	Estimated % Agreement	Lower CI*	Upper CI*
03			
Xenon images with matched Technegas image views	76.15	72.27	79.64
Xenon images with all Technegas image views	75.66	71.73	79.20
04			
Xenon images with matched Technegas image views	70.74	66.41	74.72
Xenon images with all Technegas image views	69.10	64.48	73.20
05			
Xenon images with matched Technegas image views	80.09	76.40	83.33
Xenon images with all Technegas image views	79.56	75.65	82.99

Source: Interim Blinded Read Report; Protocol CYC-009, Table 6.3.1
* 97.18% CI
Abbreviations: CI, confidence interval; FAS, Full Analysis Set; GEE, generalized estimating equation

Source: Table 8 from FDA NDA/BLA 021164 Multi-Disciplinary Review for March 26, 2020 submission, DARRTS June 25, 2021.

5 Risk Assessment & Safe-Use Conditions

The review team's assessment of safety is based on data (N=291) from four Applicant conducted clinical studies. The review team also evaluated data from 138 publications (which totaled in approximately 17,800 patients) in Technegas clinical investigations, as well as the review of postmarket reports. Table 3 lists the clinical studies that support the safety database.

Table 3 Applicant Clinical Studies to Support Safety

Trial Identity	Trial Design	Regimen/ Schedule/Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries
Controlled studies to support efficacy and safety						
CYC-009	Applicant-conducted within-subject noninferiority trial of Technegas ventilation imaging compared to Xe-133 ventilation imaging.	Inhalation of Technegas to reach 1500-2500 cps Inhalation of Xe-133 gas in accordance with the standard of care	Demonstrate noninferiority of Technegas compared with Xe-133 V/Q planar imaging studies	200	Subjects who have been referred for ventilation scintigraphy for any medical reason	10 (U.S.)
Controlled studies to support safety						
VM-002-01	Applicant-conducted, open-label, multicenter study in adults referred for a ventilation study as part of standard care or for a known lung condition	Technegas: 1500-2000 counts/sec	Evaluate biodistribution, calculate radiation dosimetry, valuate safety	12	Adults referred for a ventilation study	2 (Australia)
VM-001-01	Applicant-conducted, multicenter, randomized, crossover study in adults who required ventilation scintigraphy as part of standard care, including those with suspected PE, COPD, and lung cancer undergoing pre-surgical evaluation for lung reduction or lung resection	Technegas: 1500-2000 counts/sec Tc-99m DTPA: 1500 2000 counts/sec (27-4300 MBq)	Compare Technegas with Tc-99m DTPA aerosol ventilation images And evaluate the safety of Technegas	124	Adults who required ventilation scintigraphy	9 (Australia, Canada)
CYC-008	Applicant-conducted, multicenter, nonrandomized, single-blind, crossover, within-subject study in adults with suspected PE	Technegas: 1500-2500 counts/sec	Compare Technegas V/Q SPECT imaging with Xe-133 V/Q planar imaging for the diagnosis of PE and evaluate the safety of Technegas	12	Adults with suspected PE	4 (U.S.)

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; IV, intravenous; MBq, megabecquerel; mCi, millicurie; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

Source: Amended from Table 4. NDA/BLA 021164 Multi-Disciplinary Review for March 26, 2020 submission, DARRTS June 25, 2021

5.1 DEATH AND SERIOUS ADVERSE EVENTS

Deaths

No deaths were reported in the four clinical studies. The Applicant has asserted that no deaths have been reported in the literature related to Technegas administration.

Serious Adverse Events

In Study VM-001-01, two subjects (0.7%) experienced four serious adverse events (SAEs) following the administration of Technegas. None of the SAEs were considered related to Technegas. No serious AEs have been reported in the literature related to Technegas administration. [e]

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.2 ADDITIONAL SAFETY CONCERNS

Decreased Oxygen Saturation

The clinical team considered decreased oxygen saturation to be a risk with this product. The design of Technegas and how it is administered puts patients at risk for decreased oxygen saturation. The rationale is that the first breath a patient takes of Technegas contains no oxygen because the carrier aerosol is argon gas. Thus, the inhalation of Technegas reduces oxygen intake and can decrease oxygen saturation. This can cause decreased oxygen saturation as there is no oxygen in that breath. However, subsequent inhalations contain proportionately more oxygen as air progressively flows into the chamber to replace the Technegas that is removed.

Three patients in study VM-001-01 and another three patients in Study CYC-009 experienced oxygen saturation <90%. In addition, 14 patients (11.2%) received supplemental oxygen before, 7 patients (5.6%) received supplemental oxygen during, and 14 patients (11.2%) received supplemental oxygen after Technegas administration in Study VM-001-01. One patient (8.3%) in Study CYC-008 and 55 patients (38.5%) in Study CYC-009 received supplemental oxygen during Technegas administration. No patients in Study VM-002-01 received supplemental oxygen. Overall, approximately 22% of treated patients in the four clinical studies required supplemental oxygen during Technegas administration.

Patients who experienced decreased oxygen saturation during Technegas administration were able to inhale room air or have an administration supplemental oxygen and this was adequate to reduce the dyspnea and hypoxia. Overall, no patient, either in premarket or postmarket studies, required additional airway intervention, including noninvasive positive airway pressure ventilation or endotracheal intubation, due to hypoxia associated with Technegas administration. Furthermore, it does not appear that the 100% argon administered during the first breath limits the amount of room air or oxygen in the alveoli during subsequent breaths, such that gas exchange is not compromised in the long-term, or even after one breath.

Due to the incidence of hypoxia and dyspnea, the review team consulted with the Division of Anesthesiology, Addition Medicine, and Pain Medicine (DAAP) to evaluate this risk and make labeling recommendations. The review team concurred with DAAP's assessment that labeling language would be sufficient to mitigate this risk.[f] Their recommendations will be discussed below in Section 8.

Radiation Exposure Risk

Due to the radioactive nature of the product there is an exposure risk. There was none reported or discussed in the clinical review. This is a class wide risks for medications used for this purpose.

[f] Consultation Memorandum. Renee Petit-Scott, MD Medical Officer, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), darrted 10/9/2020.

6 Expected Post Market Use

If approved, Technegas will be used in adults and children undergoing evaluation for PE in both the inpatient and outpatient setting. The procedure would be under the supervision of diagnostic nuclear radiologists or nuclear medicine physicians. They, and the healthcare staff working in the facility, would be aware of the risk and have proper interventions on site, in this case supplemental oxygen.

7 Proposed Risk Management Activities

The Applicant did not propose any risk management activities beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Review Team has determined that REMS is not necessary to ensure the benefits of Technegas outweigh the risks. The safety issues of dyspnea and hypoxia has been reviewed and consulted on with DAAP. These risks will be communicated in the PI. The PI will include two *Warnings and Precautions*. One is for dyspnea and hypoxia. The other for radiation exposure risk. As mentioned, DAAP agreed with this labeling proposal and assisted with the language when consulted.

For the risk of decreased oxygen saturation, the recommendation will be to monitor oxygen saturation with continuous pulse oximetry and allow patients to breathe room air throughout the procedure. Providers should consider supplemental oxygen before and at any time during the procedure if indicated. Since patients will be having this administered for a V/Q scan, they essentially have suspected pulmonary pathology at baseline so as such, the medical facility will be designed and prepared to manage respiratory related problems. The facility will have equipment and the providers will have awareness and know what interventions are needed and how to support patients that may have decreased oxygen saturation. Furthermore, for most patients the use of room air after the first breath generally resolves the transient hypoxia that occurs. As discussed, although supplemental oxygen was given, no airway support interventions were required.

The radiation exposure risk is a class risk and the healthcare team will also have knowledge about safe handling procedures and protecting patients.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Technegas to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Imaging and Radiological Medicine have any concerns or questions, or if new safety information becomes available, please send a consult to DRM.

10 References

[1] J Bělohlávek, V dytrych, a linhart. pulmonary embolism, part I. epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. exp clin cardiol 2013;18(2):129-138.

[2] Bajc, M, JB Neilly, M Miniati, C Schuemichen, M Meignan, B Jonson, and E Committee, 2009, EANM guidelines for ventilation/perfusion scintigraphy : Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography, Eur J Nucl Med Mol Imaging, 36(8):1356-1370.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	022335
Action Goal Date	June 26, 2021
OSE RCM #	2020-695
Reviewer Name(s)	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	May 26, 2021
Subject	Evaluation of Need for a REMS
Established Name	Technetium Tc-99m carbon aerosol
Trade Name	Technegas
Name of Applicant	Cyclomedica Australia Pty Ltd.
Dosage	Technetium 99 labeled carbon aerosol for inhalation; single ingredient product
Division	Division of Medical Imaging and Radiation Medicine (DMIRM)

This memo by the Division of Risk Management (DRM) defers the review as to whether a risk evaluation and mitigation strategy (REMS) for the new drug application (NDA) 022335 Technegas (technetium Tc-99m) is needed to ensure its benefits outweigh its risks. Cyclomedica Australia Pty Ltd (the Applicant) submitted a 505(b)(2) NDA for a novel drug-device combination product that uses the TechnegasPlus Technegas Generator and (b) (4) carbon crucible to formulate Technetium Tc-99m carbon aerosol.

On March 26, 2020 the Applicant submitted the NDA for technetium Tc-99m for the proposed indication for use in functional lung ventilation imaging (b) (4) A major amendment was filled on February 26, 2021 for review of the Applicant's chemistry and manufacturing control (CMC) issues, extending the goal date to June 26, 2021.

Upon review of the amended application from the Applicant's submission on February 26, 2021, the DMIRM has determined that this NDA cannot be approved in its present form and will get a complete response (CR) due to issues regarding the drug substance and drug product. At this time the DRM cannot make a recommendation on whether a REMS will be needed for this product. We will re-assess this NDA upon resubmission, provided the Applicant adequately responds the recommendations DMIRM has provided.

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