CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022335Orig1s000

OTHER ACTION LETTERS

NDA 022335

COMPLETE RESPONSE

Cyclomedica Australia Pty Ltd.
Attention: Karen Wolfe-Kerker,
Vice President, Regulatory Affairs
Certus International, Inc
1422 Elbridge Payne Road, Ste 200
Chesterfield, MO 63017

Dear Ms. Wolfe-Kerker:

Please refer to your new drug application (NDA) dated March 26, 2020, received March 26, 2020 and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Technegas™ Technetium Tc-99m carbon aerosol.

We acknowledge receipt of your major amendment dated February 26, 2021, which extended the goal date by three months to June 26, 2021.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The Approvability Issues (deficiencies), with recommendations to address them, are as follows:

A. Drug Substance and Drug Product

1. Characterization and control of the aerosol drug

In the current review cycle, the NDA has not provided adequate characterization of the aerosol, including aerosol composition, batch formula, batch data, stability data, identity, strength, purity, delivered dose, generator yield, generator duty cycle and generator recertification period. You have not established aerosol critical quality attributes and specifications to ensure the identity, strength, quality, purity, or potency of the drug product under 21 CFR 314.50(d) (ii)((a)). This includes attributes, methods and acceptance criteria.

To address this issue, you must develop a quality program to characterize and control your Technegas aerosol drug product. Validate your aerosol production method at the highest and lowest end of the radioactivity range that you load to the crucible and measure particle size distribution, radioactivity of the aerosol and yield of the aerosol in this range. Propose and describe analytical methods suitable for their intended purpose, with appropriate validation. Establish specifications and justify acceptance criteria for the critical product quality attributes based on data. Submit results from at least three production runs at the minimum and maximum radioactivity load of your range.

2. Validation of the aerosol drug production and documentation

To address this issue, as outlined in Approvability Issue #1, provide aerosol batch data from validated analytical methods for at least three registration batches to support your commercial aerosol drug production and in-process controls at the minimum and maximum crucible load of sodium pertechnetate radioactivity. The batches must meet specifications and be produced according to the proposed regulatory commercial production process under the in-process controls using sodium pertechnetate injection solution supplied by the three manufacturers approved in the United States (Technelite, Ultra-TechneKow and Radiogenix). Revise your regulatory production description as advised in the Discipline Review Letter sent December 7, 2020. As advised, implement the following revisions: remove (b) (4), include the volume and strength of the sodium pertechnetate injection solution loaded in the crucible, include the percent yield based on batch data produced at minimum and maximum range of radioactivity loaded in the crucible and remove the statement, (b) (4) ."

3. Analytical methods to characterize the aerosol particle size distribution, radioactivity and the aerosol yield

To address this issue, as outlined in Approvability Issue #1, develop validated analytical methods which are suitable to characterize the aerosol drug particle size distribution, radioactivity and the aerosol yield. Due to the short expiry (10 minutes) and radioactivity of the aerosol, standard analytical methods for pharmaceutical aerosols may not be suitable for this product. Consequently, analytical methods may need to be developed for drug product quality, such as those described in literature. For example, Jérémie Pourchez etal, *Generation and characterization of radiolabeled nanosized carbonaceous aerosols for human inhalation studies*, Journal of Aerosol Science, Elsevier,2013,55, pp.1-11. 10.1016/j.jaerosci. 2012.07.011. For each method, submit the analytical method description and the method validation. We recommend you partner with radiopharmaceutical drug development experts to develop and validate your new methods and to submit the necessary documentation to the NDA to meet requirements of drug regulations.

4. Control of a Critical Component of the Radioactive Drug Substance (Crucible)

In the current review cycle, the NDA has not provided adequate specifications for the crucible, on release or stability. Batch data, stability data and a post-approval stability protocol for the crucibles have been agreed upon but not provided. To address this issue, develop a quality program to characterize and control your crucible, which is a critical component of the radioactive drug substance. Revise your crucible specifications as advised, submit crucible release and stability data which meet specifications, and submit a stability protocol for the crucible.

B. PROCESS:

5. Environmental Controls

Your current environmental controls within the crucible manufacturing suite are inadequate. The crucible manufacturing process (b) (4) to assure crucible product quality. We recommend a minimum of (b) (4) environmental controls be established and monitored with (b) (4) prior to packaging to meet the requirements of 21 CFR Part 211.46.

6. Inadequate manufacturing control strategy for (b) (4) Crucible:

In the current review cycle, the NDA has not established adequate controls at each stage of the crucible manufacturing process related to validated operating parameters, in-process controls to support critical quality attributes. Additionally, there are gaps with regards to raw data generation, storage and documentation of regulated data using (b) (4) for manufacturing of (b) (4) Crucible.

To address this issue, please consider the following:

(b) (4)

(b) (4)

[redacted]

7. Shipping

We acknowledge the ISTA study protocol and test reports submitted on1/7/2021 for the crucible shipping studies; however, you have failed to address the adverse test observations noted for the tests. You have failed to propose corrective actions or any proposed design changes for the primary or secondary packaging to address the deficiencies for the (b) (4) crucibles. Provide updated test reports, address test observations, detailed corrective actions with any proposed packaging design changes for primary and secondary packaging for review and approval. Any packaging change will require a new shipping study.

8. Production

We acknowledge the constraints of conducting functional tests for the final drug product with each device release; however, you have failed to demonstrate consistent and reliable production of the Tcm-99 carbon aerosol under good manufacturing conditions and documented registration batches to comply with the requirements of actual yield and % of theoretical yield as required by 21 CFR Part 211.103 applicable for the Technegas System. Additionally, this a requirement under 21 CFR Part 4 if adopting the streamlined approach and implementing 21 CFR Part 820 regulations as the quality system.

9. Reliability Assessment

Your reliability assessment report for the Technegas™ system (val-003) is not acceptable since it is not based on an approved protocol /verification test but exclusively on customers complaints data gathered by the firm. Submit the verification protocol, analytical tests/ methods, specifications and acceptance criteria and final report for review and approval.

10. Yield

We acknowledge frm-0077 Technegas™ maintenance and repair check list and the mnl-004 us tp preventive maintenance instruction submitted on 2/26/2021

to be executed during annual recertification to meet requirements of functional test for the device for tcm-99 carbon aerosol; however, the proposed procedures do not address the concerns of on-going yield monitoring of the final drug product by the Technegas™ system as approved in drug specification.

C. DEVICE:

11. Exposure Dose

Provide details on the calculations performed in determining exposure doses and threshold values that were used in calculating margin of safety values for all detected chemicals. This information can be provided in tabulated form for instances where the same calculation was repeated, however, explanatory notes should be provided to describe and justify the selection of specific values including but not limited to measured analytical concentrations, exposure metrics (e.g., assumed maximum breathing volumes), conversion factors, toxicity threshold values, and uncertainty factors.

D. CLINICAL

12. Risk of Dyspnea and Hypoxia

Raw data submitted from the CYC-009 study indicate that only 21% of subjects inhaled Technegas without operator intervention to provide supplemental oxygen or to interrupt Technegas flow for the subject to breath room air. You have proposed that adult patients should be instructed to (b) (4) A clear upper time limit for Technegas administration and instructions for the operator to provide room air and supplemental oxygen before, during, and/or after Technegas administration are lacking in your NDA. Also lacking is discussion of breathing instructions for optimal or near-optimal risk mitigation and instructions for operators to monitor and prepare for this risk. Therefore, you will need to include the following information in your complete response:

a. For each patient breathing method:

   i. Specify or estimate the proportion of CYC-009 subjects who used this method alone or in specific mixture of methods

   ii. Clarify the relationship to methods studied in other investigations, including NDA022335\0001\m5\54-lit-ref\lloyd-1994-2.pdf and NDA022335\0001\m5\54-lit-ref\james-1991c.pdf

iii. Discuss data on relative advantages and disadvantages to the patient for maximizing the likelihood of targeted biodistribution and minimizing the risk of dyspnea and hypoxia

b. Add the information lacking in the current NDA to instructions for prescribers and device operators and add or re-prioritize patient breathing instructions based on analysis specified under Issue #3a.

13. Recommended Loading Range in Adults

Justify the same or a revised range for your recommended loading range of (b) (4) sodium pertechnetate Tc 99m injection, USP, accounting for the range, volume, and number of loadings actually administered in study CYC-009. If gaps remain between studied and recommended use, provide a discussion of operator and patient tradeoffs for justification of each gap. Also note our recommendation to cover the to-be-marketed range of sodium pertechnetate Tc 99m loadings from minimum to maximum when conducting new CMC investigation under CMC Issue #1.

14. Recommended Loading Range and Lung Count Rate In Pediatric Patients 6 Years of Age and Older

Justify the same or a revised range for recommended lung count rate of 500 cps to 1000 cps and loading range (b) (4) accounting for data on these parameters in actual use. Provide range estimates with source information for the total number of pediatric patients 6 years of age who have received Technegas in total in both of the following populations:

a. Investigations reported in published literature.

b. Post-market experience where Technegas is marketed, either based on marketing information available to you or on estimation from a surveyed sample of Technegas administrators focused on pediatric patients.

Please note our recommendation to cover the to-be-marketed range of sodium pertechnetate Tc 99m loadings from minimum to maximum when conducting new CMC investigation under Product Quality Issue #1.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR*

Requirements for Prescribing Information[1] and *Pregnancy and Lactation Labeling Final Rule*[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at *http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm*

PROPRIETARY NAME

Please refer to correspondence dated, November 25, 2020, which addresses the proposed proprietary names, (b) (4) and Technegas. These names were found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

During a recent inspection of the Cyclomedica Australia Pty Ltd (FE1#3009638066) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility that were conveyed to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the supplemental application data.
   - Include tables that compare frequencies of adverse events in the supplemental application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the dropouts from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the supplemental application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at 301-796-1348.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

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/

CHARLES J GANLEY
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