CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208700Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208700

COMPLETE RESPONSE

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated April 27, 2016, received April 28, 2016, and your October 18 and 19, 2016, amendments, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for LUTATHERA (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial.

We have completed our review of this application 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.

CLINICAL/STATISTICAL

1. FDA is not able to verify the data submitted in NDA 208700 due to missing data, uninterpretable data, data errors and unusable datasets. In order for FDA to evaluate the safety and effectiveness of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, and to verify data proposed in product labeling, submit datasets from all studies included in the NDA submission that are accurate, complete, and internally consistent in order to allow FDA inspection, review, and archiving. A comprehensive review of all data submitted in the NDA was not possible due to the deficiencies catalogued above; therefore, additional deficiencies may exist that were not discovered during the course of the review.

   In addition to providing accurate, complete, and internally consistent datasets, ensure that the following deficiencies are addressed in your resubmission:

   a. Provide datasets with English characters, including variable names (for example, the variable names were in Chinese character *Adverseeventsm1* data under SN 22).

   b. The legacy raw datasets appeared to be modified after the clinical data cut-off date (for example, DM information was last modified on November 14, 2015, and the most recent tumor evaluation was modified on September 23, 2016). Ensure

that the raw data used to generate the datasets have been audited for completeness, missing data and errors, and provide cleaned and locked data up to the time of database lock.

c. Minimize missing data or provide justification for why these data are not included. For example:

   i. Essential variables for tumor assessments were missing.

   ii. Baseline CrCl values or dosing information for several patients in the fdaclinpharmreqbaselab dataset were missing. Dosing information (for example, tdosemci) was missing even though organ radiation exposure and blood concentration (Cmax, AUC) data were provided.

   iii. Demographic and baseline patient characteristics data were missing (for example, in the fdaclinpharmreqbaselab dataset).

   iv. Laboratory parameters and organ exposure information was missing from clinical pharmacology datasets in the Erasmus PK study folder.

d. The datasets contained values that appeared to be incorrect or invalid. For example, some laboratory test results appeared to be grossly out of range and incompatible with other reported data for the same patient. Furthermore, some lab test values did not have measurement units associated with them to permit an understanding of the meaning of the value. Ensure that the data are reviewed for errors and provide appropriate units of measurement for all data values.

e. The datasets are missing unique subject IDs and study IDs. Ensure that all datasets submitted in the NDA include these variables and assign each patient a single unique subject identification (USUBJID) across the entire submission.

f. Ensure that consistent doses are recorded across datasets (for example, for patient BE01-002: 7.541 GBq in fdaclinpharmreqbaselab and 7.274 GBq for pktp datasets). Provide consistent data across datasets or justify why there are different doses provided.

g. In order to confirm the derived values/parameters, provide the following variables (sampled, timefadm, measurdt, bloodvol, sampvol, collvol, countval, countvau, activcon, pepticon, activity, percia, and percumia) in the Erasmus datasets, or justify why the variables cannot be provided: pp, pc, supppc, and supppp datasets.

2. Submit revised clinical study reports (CSR) that contain data and analyses based on the datasets submitted to address item number 1.

3. As required per 21 CFR 314.50, provide safety and efficacy subgroup analyses for gender, age, and racial subgroups. Also provide subgroup analyses based on stratification factors and any other important disease characteristics.

FACILITIES

4. During recent inspections of the manufacturing facilities for this NDA, our field investigator observed objectionable conditions at the **Advanced Accelerator Applications, Meldola, Italy (FEI#3010469290)**; **Advanced Accelerator Applications, Colleretto Giacosa, Ivrea, Italy (FEI#3010175147)**; and **IDB Radiopharmacy B.V., Netherlands (FEI#3010293768)** facilities and conveyed the information to the representatives of each of the facilities at the close of the inspections. Satisfactory resolution of the observations is required from each of the facilities before this NDA may be approved.

ADDITIONAL COMMENTS

5. Submit the following in your response:

   a. DSMB meeting minutes from the NETTER and ERASMUS trials; and,

   b. A study data reviewer's guide and an analysis data reviewer's guide for the legacy raw data and analysis data, respectively.

6. In order to facilitate re-submission of the datasets, refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf, and "Providing Regulatory Submissions In Electronic Format-Standardized Study Data and Data Standards Catalog," available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334 and http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

7. To facilitate FDA's review of the application, we recommend that you use the standards specified in the FDA's Data Standards Catalog.

8. Traceability permits an understanding of the relationships between the analysis results tables, listings and figures (TLFs) in the CSR, and the analysis datasets, tabulation datasets, and source data. To ensure data traceability, map variables in the case report forms (CRFs) to the corresponding variables in the datasets (for example, sex was reported as 916576 and 920197 but reported as Male and Female in aCRF for variable DM.DMSEX). Additionally, provide information necessary to allow FDA to understand the provenance of the data (i.e., traceability of the analysis results back to the annotated CRF).

9. Provide a define file that allows reviewers to understand the variables and derivations in the datasets. Additionally, ensure that the define file has sufficient comments, adequate bookmarks, and hyperlinks to the xpt files, CRFs, controlled terminologies, and

computational methods. The define files submitted to the NDA were missing metadata and there were inconsistencies between output variables and the assigned code.

10. Provide consistent definitions and patient numbers between datasets or explain why the discrepancies should be accepted (for example, "A" indicates treatment in fdaclinpharmreqbaselab database, but "AO" is listed as treated in the PK sub study in summpat database).

11. Provide consistent controlled terminology across datasets (for example, yes vs. no value was coded as no vs. yes; the treatment arms were coded as A vs. B in PFS.treat and 1 vs. 2 in PFS.treatx without control terminology for PFS.SAS7bdat).

12. Provide all necessary SAS programs, SAS macro, SAS format library, and adequate documents in order to duplicate the analysis datasets derivation from the raw dataset and the analysis results in the CSR and USPI.

13. Provide an explanation for why the calibration factor (b) (4) is used in the gamma detection of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the following patients in the pktp dataset: DE01-006, DE01-009, DE01-010, and DE01-014, as other patients in this dataset have a calibration factor ranging from (b) (4) to (b) (4).

14. Provide the analysis for patient ID NETTER-1-UK06-003 in the pp and supppp datasets.

15. The submitted datasets had many missing essential variables precluding our ability to accurately assess efficacy. Ensure that efficacy datasets include stratification variables based on IVRS in addition to those based on the CRFs. In addition, include age, race, gender and important disease characteristics as variables.

16. Provide datasets in XPT format to allow FDA to process, review and archive the data. Specifically, ensure that the following issues are addressed in the submission.

    - Split datasets to ensure that datasets are no larger than 5 GB [four datasets (Labblood, eortc, laburinem2, and adverseeventm1) were greater than 5 GB in size].
    - To reduce file size, set the allotted length for each variable to the maximum length of variables used across the entire submission.
    - Include one dataset per transport file with the same name.
    - Set the maximum length in characters for dataset and variable names to 8.
    - Set the maximum length in characters for dataset and variable labels to 40.

17. Use American Standard Code for Information Interchange (ASCII) text codes. We recommend that you utilize the default SAS coding system, wlatin1 (i.e., western world encoding) because the encoding system you used to generate the datasets (utf-8 Unicode) resulted in reading errors.

- Exclude punctuation, dashes, spaces, non-alphanumerical symbols, and special characters in variable and dataset names.
- Exclude user-defined SAS format libraries. Instead, you may provide this information in the Controlled Terminologies.

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 product under consideration regardless of indication, dosage form, or dose level.

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

19. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    a. Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    b. Present tabulations of the new safety data combined with the original application data.
    c. Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

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

21. 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.

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

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

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

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

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* and *Pregnancy and Lactation Labeling Final Rule* 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.

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 under 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ("the Program"). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action

on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Susan Truitt, Regulatory Health Project Manager, at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
12/19/2016