CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200655Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200655

COMPLETE RESPONSE

The Feinstein Institute for Medical Research
Attention: Thomas Chaly, Ph.D., FAIC
Chief, Cyclotron – Radiochemistry Department
350 Community Drive
Manhasset, NY 11030

Dear Dr. Chaly:

Please refer to your New Drug Application (NDA) dated October 29, 2009, received October 30, 2009, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluorodopa F 18 Injection, 0.42 mCi/mL to 8.33 mCi/ml.

We acknowledge receipt of your amendment dated December 15, 2015, which constituted a complete response to our October 22, 2013, action letter.

We acknowledge receipt of your major amendment dated April 11, 2016, which extended the goal date by three months.

We also acknowledge receipt of your amendment dated August 31, 2016, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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.

CLINICAL / STATISTICAL

Your resubmitted application contained the report of the prospectively designed "Study #17" which aimed to evaluate Fluorodopa F 18 for: 1) sensitivity, specificity, and clinical utility in the differential diagnosis of Parkinsonian syndromes, 2) inter-reader reliability, 3) quantitative correlation with Parkinson's disease diagnosis, and 4) safety by monitoring for adverse events. This study does not provide sufficient confirmatory evidence of effectiveness and the Fluorodopa F 18 PET scan's performance is not adequately characterized.

In Study #17, 45 movement disorder patients were imaged with Fluorodopa F 18. Of these patients, 32 had images interpreted as positive for visualization of a loss of dopaminergic neurons in striatum and 13 were interpreted as negative.

Out of these 13 patients, only 5 patients had undergone a clinical follow up which was to serve as a standard of reference and only 1 of these patients had a clinical follow up at a pre-defined time interval following the Fluorodopa F 18 PET scan (>1 year). Some patients had an interval as short as one or two weeks. Therefore, out of 13 patients with no loss of dopaminergic neurons in striatum as visualized with Fluorodopa F 18, only 1 patient had this interpretation adequately verified.

Additionally, the image interpretations were known to the clinicians providing follow-up prior to their determination of the clinical diagnosis. Because the clinician was responsible for making the assessment of the clinical diagnosis, which served as the standard of reference, it is possible that the results of the test influenced their assessment. This is not acceptable as a standard of reference and is not adequate for support of the proposed visualization claim.

Furthermore, we note that in patients with "positive" images, only 20 patients had a standard of reference obtained 1 year or more following imaging with Fluorodopa F 18. Most patients did not have 1 year of follow-up. This is also inadequate.

The three readers agreed with each other on the interpretation of the scans in 98% (44 of 45 images) of the patients. It is not clear what clinical information was provided to the readers or the amount of independence from each other they had in making the reads.

Going forward, it is important to develop a plan to address these deficiencies. It will need to include a method to make a clinical assessment of the patients' clinical diagnosis that is not influenced by the results of the image reads. This will include obtaining complete follow up on all of the subjects. You may extend Study #17 to enroll additional patients who will also go on to have a clinical follow up at a pre-defined interval as an adequate standard of reference. The deficiencies with the study protocol and conduct of the study will need to be corrected as you go forward. You should also clearly document which clinical features in each patient were consistent with Parkinsonian or non-Parkinsonian syndrome.

You may consider requesting a meeting to discuss the design of an appropriate statistical analysis plan for the completion and extension of Study #17.

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

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.

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 original application data.
    - Include tables that compare frequencies of adverse events in the original 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 drop-outs 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 original 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.

ADDITIONAL COMMENTS

We have the following comment which is not an approvability issue:

As per your amendment dated April 14, 2016, we remind you of your commitment to provide information regarding (b) (4) [redacted]. You agreed to submit this information in a Prior Approval Supplement if NDA 200655 is approved. However, we acknowledge your amendment dated August 31, 2016, containing chemistry information to address this commitment. As noted above, your August 31, 2016 amendment was not reviewed for this action and may be incorporated by specific reference if you decide to resubmit this application.

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.

If you have any questions, contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager at (301) 796-1427 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Charles J. Ganley, M.D.
Director
Office of Drug Evaluation IV
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/

THUY M NGUYEN
09/15/2016

CHARLES J GANLEY
09/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200655

COMPLETE RESPONSE

Thomas Chaly, Ph.D., FAIC
The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry Facility
350 Community Drive
Manhasset, New York 11030

Dear Dr. Chaly:

Please refer to your New Drug Application (NDA) dated October 29, 2009, received October 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluorodopa F 18 Injection.

We acknowledge receipt of your amendments dated January 26, February 5, April 14, June 16, July 28, and September 27, 2010; November 9 and December 12, 2011; January 19, February 7, March 14 and 21, April 11, 17, and 18, October 22 and 23, November 13, and December 17, 2012; January 3, 14, and 16, April 5, June 7, July 19, August 13 and 21, September 16, and October 10, 2013.

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.

CLINICAL / STATISTICAL

Your application contains no data from adequate and well controlled clinical trials. Significant deficiencies have been identified in the referenced literature studies and in the studies you have conducted in support of this application. The data submitted in your application are not sufficient for evaluating the diagnostic effectiveness and usefulness of Fluorodopa F 18 PET in the proposed patient population.

1. The following deficiencies have been identified with clinical Study #15, which was conducted at the Feinstein Institute of Medical Research:

   a. The study is a retrospective, single center study.

   b. The study was not conducted according to a pre-specified protocol, and hence, definitions of the primary efficacy endpoint and the standard of truth that would normally be specified by a protocol, are not well-defined for the study.

c. The study used each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. We do not find such a standard to be clinically meaningful and do not agree with the cited diagnostic performance measurements of Fluorodopa F 18 as 100% for sensitivity and 100% for specificity.

d. Of the 185 study patients, 158 patients had a pre-imaging clinical diagnosis of Parkinson's disease and were responding to Parkinson's disease medications. For these patients a Fluorodopa F 18 PET scan provides no additional clinically useful information. Deficiencies concerning the remaining 27 study patients are discussed below (Study #16).

e. You have provided no documentation that Fluorodopa F 18 PET images have been read independently by three readers blinded to clinical information. Furthermore, inspection of the study site revealed that none of the 47 audited cases contained documentation that each patient's images were read by three blinded readers.

2. Study #16 is a publication with the follow-up results of 27 Fluorodopa F 18 PET negative patients enrolled in Study #15. Study #16 has the following major deficiencies:

   a. Per your amendment dated April 5, 2013, only 8 of the 27 Fluorodopa F 18 PET negative patients from Study #15 were followed for 2 to 4 years to obtain the patient's final clinical diagnosis. Clinical data from such a small number of patients do not provide a reliable assessment of the performance characteristics of Fluorodopa F 18 PET. Furthermore, inspection of the study site revealed that none of the subject files contained documentation (clinical follow-up confirmation) of the continued absence of classical Parkinson's Disease symptoms and signs.

   b. The reasons for not obtaining follow up on the remaining 19 patients are not provided.

3. Among the remaining literature publications in your application (Studies #17-23), only the publication by Eshuis et al. (Study #21) provides clinical data for the assessment of the efficacy of Fluorodopa F 18 as a diagnostic radiopharmaceutical. However, Study #21 does not provide substantial evidence of efficacy for the following reasons:

   a. The study is a small single center study and is exploratory in design.

   b. All study patients had a diagnosis of Parkinson's disease at the time of enrollment. The study excluded patients with atypical signs and patients not responding to Parkinson's disease medication. Therefore, the study does not evaluate a patient population that might benefit from a diagnostic imaging test.

   c. The definition of positive scans (mean standard uptake value in patients below two standard deviations of the mean in healthy controls) is an exploratory quantitative measure and its threshold is arbitrarily set.

d. It is unclear how specificity was calculated, as all patients included in the analysis of the study had confirmed Parkinson's disease.

To address these deficiencies, we recommend the following:

1. Conduct an adequate and well-controlled clinical trial which might provide substantial evidence of effectiveness of Fluorodopa F 18 in the intended patient population. We encourage you to develop such a study using a pre-defined standard of reference for measuring the performance characteristics (sensitivity and specificity) of Fluorodopa F 18, a pre-specified statistical analysis plan, and image interpretations made by independent readers blinded to clinical information. Note in order to measure the sensitivity and specificity of Fluorodopa F 18, you need to obtain the standard of reference (follow-up clinical diagnosis) in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients. You should use as a standard of reference the clinical diagnosis made by a movement disorder specialist at a predefined time interval following the Fluorodopa F 18 PET scan.

2. The study population must include subjects who might benefit from the Fluorodopa F 18 PET scan. Such patients could include those in whom Parkinsonian and essential tremor could not be differentiated on clinical grounds, those with suspected early onset of Parkinsonian syndrome, and/or those not responding to a Parkinson disease medication.

   To facilitate the interpretation of the study's results, we recommend that you consider exclusion of subjects with features suggestive of multiple system atrophy or progressive supranuclear palsy, response to Parkinson's disease medication, a clinical history exceeding five years, and concomitant medication known or suspected of interacting with striatal uptake of Fluorodopa F 18.

3. We reference the Good Clinical Practice (GCP) deficiencies identified during our inspection of your clinical study site and communicated to you on March 22, 2013. These deficiencies call into question the reliability of the clinical data in your application. It is necessary to conduct a study in compliance with GCP standards to ensure the quality and integrity of the data.

GOOD CLINICAL PRACTICE (GCP) INSPECTION

A GCP inspection was performed at the clinical site where Studies #15 and #16 were conducted. As noted during the inspection, a prospective study protocol and case report forms were not used and important study records (including source records) were not available for inspectional review. Additionally, the adequacy of clinical safety monitoring could not be determined. As a retrospective documentation of the clinical experience at a single center, these studies do not appear to have been performed under adequate GCP standards sufficient to support a regulatory submission.

During the inspection of your clinical study site, deficiencies were conveyed to you for failure to prepare and maintain adequate case histories and for inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects. The following is a detailed description of these deficiencies:

1. Referral diagnoses were not adequately documented as part of subject case records. The subject files did not contain the physician referral letter in 15 of the 47 files audited. The files typically lacked documentation of the presence of the cardinal features of Parkinsonian syndrome and/or responsiveness to Parkinson's disease drugs.

2. The case records for the control subjects did not include evidence of an adequate neurological examination by a qualified neurologist.

3. For all the subjects audited, the case records lacked evidence of PET scan interpretation by three separate blinded readers.

4. Study treatment and procedures were not adequately documented. For example, there was no documentation of carbidopa administration prior to Fluorodopa F 18 in a total of 18 of the subject files audited and the use of concomitant medication was inconsistently documented.

5. For Study #16, none of the subject files contained documentation (clinical follow-up confirmation) of continued absence of classical Parkinson's disease symptoms and signs.

6. For Study #15, the available study records indicated that the PET scan procedure was discontinued in one subject due to an undocumented adverse event. This observation is inconsistent with your claim of no adverse events in the study.

PRODUCT QUALITY

You have not adequately responded to our requests for information dated December 28, 2012 and May 31 and July 2, 2013. The following issues remain outstanding:

1. Regarding specifications for the precursor of the drug substance, add a test method and acceptance criteria to establish the chiral identity of the precursor (i.e., the L-isomer only). Provide experimental and characterization data including optical rotation measurements for the precursor to the drug substance adequate to justify the proposed acceptance criteria.

2. Provide the revised drug product specifications, in tabular format, in the appropriate drug product section of your NDA (Section 3.2.P.5.1 Specifications). A separate discussion of drug substance specifications in the drug substance section of the NDA is not necessary. Describe all analytical methods in the drug product section 3.2.P.5.2 Analytical Procedures. Provide a revised document with tracked changes identified.

3. Regarding the pH of the product, [redacted] (b) (4)

4. Provide validation data in the drug product section of your application for the drug product HPLC chemical and chiral purity method establishing the limit of detection and quantitation, accuracy, precision, linearity and robustness. This data was not included in your August 21, 2013 amendment, as stated in your cover letter.

5. [redacted] (b) (4)

6. [redacted] (b) (4)

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise the labeling, 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

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.

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 the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA 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 drop-outs 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 original NDA 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.

ADDITIONAL COMMENTS

We have the following product quality related comments/recommendations that are not approvability issues:

1. (b) (4)

2. [redacted] (b) (4)

3. [redacted]

4. You have indicated that the [redacted] (b) (4) system is being qualified for bacterial endotoxins testing. If you intend to use this assay system for product release, you are reminded to submit for review, prior to implementation of the test, the summary reports of the product specific qualification of this assay.

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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 the FDA and Sponsors or Applicants," May 2009 at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf, in triplicate hard copies along with an electronic copy on CD-Rom or solely electronic submission via Gateway, as with all formal submissions to the Division of Medical Imaging Products.

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. 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.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. 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, contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager, at (301) 796-1427 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shaw T. Chen, M.D., Ph.D.
Deputy Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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

/s/

THUY M NGUYEN
10/22/2013

SHAW T CHEN
10/22/2013