CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217186Orig1s000

OTHER ACTION LETTERS

NDA 217186

COMPLETE RESPONSE

Impax Laboratories, LLC
Attention: Candis Edwards
SVP Specialty Regulatory Affairs
400 Crossing Blvd. Third Floor
Bridgewater NJ 08807

Dear Ms. Edwards:

Please refer to your new drug application (NDA) dated August 31, 2022, received August 31, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Crexont (carbidopa and levodopa) Extended Release Capsules 35/140 mg, 52.5/210 mg, 70/280 mg, and 87.5/350 mg.

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.

(1) Based on results from the relative bioavailability studies, IPX203-B16-01, IPX203-B16-05, and IPX203-B14-02, an adequate scientific bridge was not established for the carbidopa pharmacokinetic (PK) exposure between IPX203 and Sinemet or Rytary at the highest proposed dosage regimen of Crexont, although an adequate scientific bridge was established for the safety of levodopa based on PK exposure. The exposure of carbidopa from Crexont is substantially higher than that from Sinemet or Rytary; therefore, it is not possible to rely on FDA's finding of safety for Sinemet or cross-reference Rytary for the safety of carbidopa for the approval of Crexont. Thus, the safety information from your clinical trials must be adequate to support the safety of chronic exposure to the higher levels of carbidopa that patients would receive with Crexont compared with these two listed drugs.

Furthermore, the long-term safety database is insufficient to adequately characterize the long-term safety of Crexont for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. As stated in the pre-NDA meeting minutes dated March 8, 2022, the Division expected your NDA submission to have at least "a minimum number of 100 patients treated for one year with at least 50% of patients using the highest dose intended for labeling" to adequately characterize the safety of Crexont for its intended use, especially if an adequate bridge to the reference products was not established. Your NDA submission contains data for only 67 patients with 12-month exposure to Crexont

at any dose by modal dose and no patients who were exposed to Crexont at or above the highest proposed dosage regimen ((b) (4) daily) for 12 months based on modal doses. We acknowledge that the exposure data you presented in the pre-NDA meeting package and in the initial NDA submission using the average dose suggested a greater number of subjects with 12-month exposure at the proposed maximal dose, but these exposure calculations were not based on modal doses. The modal dose is the actual dose each patient took for the greatest number of days during their participation in the Phase 3 clinical trials of Crexont and is preferred for assessment of drug exposure, particularly in trials with long-term flexible dosing, such as IPX203-B16-02 and IPX203-B16-03. The method for assessing exposures using each patient's modal dose has also been used previously for other products.

Therefore, in the absence of an adequate scientific bridge to Sinemet and Rytary for the safety of the carbidopa component of Crexont, you will need to provide long-term safety data from 100 patients with continuous exposure to Crexont for at least 12 months, with a substantial proportion of patients using the highest dose intended for labeling, based on modal dose, to support the safety of Crexont. Alternatively, you may consider reformulating your proposed product to reduce exposure of carbidopa to levels that are comparable to a listed drug and can be supported by a relative bioavailability study. However, additional clinical studies may still be needed.

(2) In addition, because you are unable to rely on Sinemet or cross-reference Rytary for the safety of carbidopa in Crexont, per ICH E14 section 1.3, you will also need to conduct a thorough QT study to assess potential effects of Crexont on QTc.

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 Prescription Drug Labeling Resources[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.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

PROPRIETARY NAME

Please refer to correspondence dated, November 10, 2023, which addresses the proposed proprietary name, Crexont. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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 subject 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.

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 draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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

If you have any questions, please contact Stacy Metz, PharmD, Senior Regulatory Project Manager, at stacy.metz@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Emily Freilich, MD
Acting Director
Division of Neurology 1
Office of Neuroscience
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/

EMILY R FREILICH
06/30/2023 04:27:33 PM