



NDA 218317

COMPLETE RESPONSE

NeuroDerm, Ltd.
c/o The ProPharma Group
Attention: Ayesha Adil
US Resident Agent
Director, Regulatory Program Management
1129 20th Street, NW, Suite 600
Washington, DC 20036

Dear Ayesha Adil:

Please refer to your new drug application (NDA) (b) (4)

(carbidopa and levodopa) injection.

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 and CLINICAL PHARMACOLOGY

- (1) Based on results from the relative bioavailability study, ND0612-115, an adequate scientific bridge to levodopa based on pharmacokinetic (PK) exposure was established; however, an adequate scientific bridge was not established for the carbidopa PK exposure between Engolce and the relied-upon listed drug, Sinemet, at the highest proposed dosage regimen of Engolce. The exposure of carbidopa from Engolce is substantially higher than that of Sinemet; therefore, it is not possible to rely on FDA's finding of safety for Sinemet for the safety of the carbidopa component for the approval of Engolce. The clinical studies of Engolce were not designed to characterize the effects on the QTc interval. In the absence of an adequate scientific bridge to Sinemet for the safety of the carbidopa component of Engolce, per ICH E14 section 1.3, you will need to conduct a thorough QT (TQT) study to assess potential effects of Engolce on the QTc interval.

We note that per the proposed labeling, patients may take other carbidopa/levodopa products in addition to Engolce. If additional carbidopa/levodopa is used by patients, the overall carbidopa exposure will increase further compared to the listed drug. When designing the TQT study, you should take into consideration the carbidopa exposure from Engolce and any additional carbidopa/levodopa products, including the early morning dose

of carbidopa/levodopa, in order to identify the highest possible C_{\max} of carbidopa.

PRODUCT QUALITY

(b) (4)



NONCLINICAL

(b) (4)



DEVICE

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)

FACILITY INSPECTIONS

- (9) Following pre-approval inspection of (b) (4), listed in the application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the form FDA-483 prior to your complete response to your application. Your complete responses should include the date(s) of the facility's response to the form FDA-483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.
- (10) Following pre-approval inspection of (b) (4) listed in the application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies prior to your complete response to your application. Your complete responses should outline the corrections taken in response to the inspection. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

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

² <https://www.fda.gov/media/71975/download>

Prescription Drug Labeling Resources³ and Pregnancy and Lactation Labeling Final Rule⁴ 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.

PROPRIETARY NAME

Please refer to correspondence dated, (b) (4) which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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.

³ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

⁴ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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.

ADDITIONAL COMMENTS

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

Clinical Pharmacology

1. In your future resubmission, you should address potential concerns that may result from drug-drug interactions related to the higher exposure of carbidopa with Engolce.
2. In your future resubmission, you should provide clear labeling instructions on how to convert to Engolce from different oral carbidopa/levodopa products available on the market.

Human Factors

3. The comments in this section are not intended to convey human factors (HF) approvability issues with your proposed product; however, it will be necessary for you to consider how any revisions to your proposed product to address the deficiencies outlined above will impact your user interface.

(b) (4)



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.

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

If you have any questions, contact

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

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/

(b) (4)

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