

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203952Orig1s000**

**OTHER ACTION LETTERS**



NDA 203952

**COMPLETE RESPONSE**

AbbVie Inc.  
Attention: Matthew Kuntz, PharmD, MBA, RAC  
Director, Regulatory Affairs  
1 N. Waukegan Road  
Dept. PA77/Bldg. AP30  
North Chicago, IL 60064

Dear Dr. Kuntz:

Please refer to your New Drug Application (NDA) dated May 28, 2013, received May 28, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Levodopa-Carbidopa Intestinal Gel (LCIG).

We acknowledge receipt of your amendments dated as follows:

July 15, 2013	August 13, 2013	August 23, 2013
September 17, 2013	September 20, 2013	October 9, 2013
November 12, 2013	December 18, 2013	December 23, 2013
January 29, 2014	February 10, 2014	

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. There are deficiencies related to product quality that require additional information for validation of your revised control methods, additional dissolution profile information, and additional stability data. We require additional information concerning the specification, software, and potential hazards for the CADD-Legacy Model 1400 pump. We identified deficiencies in your human factors assessment that require modification and reassessment. You should resolve the design and engineering deficiencies concerning the pump before initiating a repeat human factors study. We have described below in greater detail our reasons for this action and, where possible, our recommendations to address these issues.

**PRODUCT QUALITY**

1. The analytical method for determining the (b) (4) should be adequately described and validated and included in the drug product specification for release and stability, with appropriate limits. It is not adequate to use this only as an in-process control listed in your Master Batch Record. Also, clarify which method ( (b) (4) ) will be used and the conditions under which the two methods would be used.

2. Provide complete stability data that includes the (b) (4) measurement to cover the 0 weeks, 5 weeks, 10 weeks and 15 weeks time points for three batches of commercial scale drug product manufactured using the (b) (4) as part of the control strategy for homogeneity of the drug product. This stability data should also include testing that demonstrates that (b) (4) does not occur with your updated control strategy. The test for (b) (4) should be described and validated and included in your stability testing. As an alternative to this (b) (4) test, you could include testing on stability to verify that the problem of appropriate levels of levodopa and carbidopa in the morning dose is continuously solved throughout the term of stability testing.
3. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). Report the dissolution data as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
4. We acknowledge your commitment to provide stability data for your drug product under frozen (-20°C) and refrigeration (5°C) conditions post-approval. However, for setting the specifications for your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point to be when the product is thawed and placed under the 5°C refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in the above comment.
5. In your October 31, 2013, response to our Information Request (IR), you indicated that (b) (4) whereas in your February 7, 2014, IR response, you indicated that (b) (4) Clarify this discrepancy (b) (4)

### **CENTER FOR DEVICES AND RADIOLOGICAL HEALTH**

1. Address the following issues regarding the CADD-Legacy Model 1400 delivery rate, delivery accuracy, and dose accuracy specifications and testing.
  - a. System delivery accuracy and bolus accuracy specifications listed in the submission are (b) (4) However, the design verification testing for the CADD-Legacy Model 1400 pump state that acceptance criteria for therapy accuracy and dose accuracy are (b) (4) and (b) (4) respectively. Clarify the correct accuracy specifications.
  - b. The design verification report (DVT-1258R-000) states that the Dose Volume accuracy specification should be updated to (b) (4) It is not clear if this recommendation was followed. Verify the Dose Volume accuracy specification and provide the supporting data. Further,

verify that the test conditions reflect the conditions the user is going to experience with respect to the pump flow rates, cassette, tubing configuration, drug temperature, and operating temperatures.

- c. Verify that infusion delivery rate and demand dose specifications are adequate for the drug dosing (e.g., minimum infusion rate, maximum infusion rate, and infusion rate increments). For example, if the maximum labeled infusion rate in the drug labeling is 10mL/hr, justification for the device specification exceeding this rate would be needed to assure that potential risks associated with a higher rate are adequately addressed.
  - d. Testing has not bracketed the infusion rates (e.g., minimum and maximum) to verify adequate performance throughout the programmable range. Provide updated testing to verify delivery accuracy at minimum and maximum programmable rates.
2. We have conducted a review of the software documentation. Provide the following software documentation for the current release version:
- a. Provide the software revision history document.
  - b. Identify any remaining unresolved anomalies and include the following information for each:
    - i. A description of the anomaly from a symptom point of view and how it is manifested,
    - ii. The location in the code where the anomaly occurs,
    - iii. A description of how to fix the code,
    - iv. A search of the software source code for other possible instances of the anomaly. For example, if the problem was an off-by-one error in an array, provide evidence that all arrays were checked for off-by-one errors,
    - v. Provide evidence that a coupling analysis was performed to identify all parts of the software that accessed the errant code and that no problems would arise because of accessing this code,
    - vi. Provide evidence that the anomalies are corrected, or provide an acceptable rationale for why the anomaly could not result in harm if it occurs,
    - vii. Provide evidence that the corrected, final finished production software was retested and that no new anomalies have been found.

- c. Provide a static analysis report for the current release version. The report should include the following:
  - i. Identify the static analysis tools used,
  - ii. Describe the implementation of the tool(s) for the analysis of the software,
  - iii. Describe the results of the testing, including any alerts/defects identified,
  - iv. Provide a detailed explanation for the acceptability of each alert/defect such that we are able to agree that it will not occur during use of the device, or does not pose a risk to health,
  - v. Provide an overall analysis and conclusion of the results.
- d. We have conducted a review of device hazards that can cause the drug infusion to occur at an incorrect rate. Column one and two in the following table identify the causes and hazard controls from the device hazard analysis documentation (MAF <sup>(b) (4)</sup>, Amendment 3, VOL 6 TAB 10B CADD-Legacy 1400 Pump Hazard Analysis). Column 3 identifies additional information needed to complete our review. Address the deficiencies identified in column 3.

<b>Hazard - Infusion delivery occurs at an incorrect rate</b>		
<b>Cause</b>	<b>Control</b>	<b>Deficiency</b>
(b) (4)		

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



## **HUMAN FACTORS**

Your human factors study report did not provide analyses and results consistent with best practice to support the review of human factors for your combination product submission. In accordance with the deficiencies that follow, we request that you implement mitigations to improve the ability of users to use your product safely and effectively and conduct another human factors study with a minimum of 15 participants, healthcare providers, and patients combined to demonstrate their effectiveness. Concerns regarding your product's design and engineering as well as comments regarding your patient and health care provider instructions for use labeling should be addressed prior to conducting another human factors study.

1. Only low battery and high pressure alarms were tested in your original human factors validation study. We noted that there are other alarms/messages that you have listed in the healthcare providers (HCPs) and patients instructions for use labeling that were not part of the study. If the response and interpretation to these alarms/messages are unique and represent critical user tasks, they should be tested, but were not tested in your original human factors validation study.
2. Your original human factors validation study showed multiple task failures for programming the pump and connecting different pump components. These failures were in addition to the reported other "operational difficulties." We are concerned that these task failures and operational difficulties can lead to suboptimal therapy, dyskinesia, loss of mobility, pain, and discomfort. We are most concerned about the following:
  - a. One HCP accidentally changed Continuous Rate value while changing Morning Dose volume.
  - b. Two HCPs failed to administer Morning Dose.
  - c. Five (5/25) HCPs and 14/25 patients experienced failures with critical tasks associated with changing the cassette.

- d. Three patients and 6 HCPs did not complete the steps for flushing the PEG-J tubing.

You have not explained how these failures and difficulties occurred such that design issues of your product can be ruled out as a cause. Therefore, evaluate the relevant data, develop appropriate mitigations, and validate those mitigations via simulated use testing.

3. You provided a supplemental human factors study to evaluate the lock levels; however, only 10 HCPs participated in the study. The study was designed to evaluate the HCPs' understanding of the differences between the lock levels. The user tasks associated with setting up lock levels were not evaluated as part of this study. Provide test results for these tasks or provide justification for the study methodology you followed. Also, clarify the specific patient characteristics for HCPs' determination of and setting the lock level for a specific patient.
4. Regarding your supplemental study to evaluate the lock levels, 15 patients were tested to perform Morning Dose and Continuous Rate adjustments. It was not clear if the scenarios in the test were designed to evaluate patients' ability to adjust dose. It was not clear if the patients are only enabled to adjust Morning Dose and Continuous Rate. We note that patient adjustments can be made between a preset prescribed dose and a pre-programming upper limit (+10% of the prescribed dose). Also, describe the minimum and maximum dose that can be prescribed, the adjustments and what parameters can be adjusted relative to the prescribed dose setting, how adjustments can be made, and how the pump tracks adjustments made by patients.
5. Your supplemental study results showed six (6/15) patients failed to inspect for tubing kinks prior to programming adjustments. In addition, some HCPs indicated confusion regarding the table that you provided in the HCP pump labeling that described the function of the different lock levels and whether Morning Dose could be adjusted in LL1. As with the other failures contained in these deficiencies, evaluate these and develop mitigation strategies for reducing them and test data to demonstrate their effectiveness.
6. Your combined instructions for use for patients included warning and precaution statements that were not included in your human factors testing. Interpreting and abiding by warnings and precautions represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings and precautions could lead to patient harm. Ensure that these instructions are optimized for safe and effective use, and that they are not simply a combination of two instructions.
7. Provide screen shots for the HCP programming tasks and patient dose adjustment tasks.

## **LABELING**

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

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

We acknowledge receipt of your submission dated May 28, 2014, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Levodopa-Carbidopa Intestinal Gel (LCIG) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

## **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 side-by-side tabulations of exposure and adverse event data for the periods covering the original ISS combined with the 120-day update, the post-action update and the grand total for post-action safety update plus the information in the combined 120 update and original ISS.
  - 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 previously unreported 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 comments/recommendations that are not approvability issues:

### **PRODUCT QUALITY**

1. Change all references from [REDACTED] <sup>(b) (4)</sup> to "carbidopa and levodopa enteral suspension" in the labeling to comply with Agency drug product dosage form naming conventions.
2. The comparability protocol to accept [REDACTED] <sup>(b) (4)</sup> with a reporting category of annual report is not acceptable. This would require prior approval labeling changes.

### **CENTER FOR DEVICES AND RADIOLOGICAL HEALTH**

1. In the device hazard analysis, there is a stated assumption that the onset of Parkinson's symptoms due to infusion delivery at an incorrect rate is detectable by the patient soon enough for the patient to stop the potentially harmful activity and adjust the dosage for improved response. Please address the following:
  - a. The occlusion detection verification testing results are measured against an acceptable pressure range, while the system specifications are provided in time to detection. Verify that the system specifications in time to detection are derived from the design verification tests using LCIG.
  - b. The occlusion detection alarm specification is 26psi +/-14psi. Describe the practical effect of having a high pressure alarm that is tripped at 12 psi. Additionally, provide justification for the deviation in pressure alarm of [REDACTED] <sup>(b) (4)</sup> psi.
2. There appear to be inconsistencies in the system specifications listed in the submission with the drug delivery requirements or device verification testing. For example, the time to occlusion alarm identifies time for [REDACTED] <sup>(b) (4)</sup> infusion rate. However, the device specification for maximum infusion rate is 20 mL/hr. Also, as mentioned, the delivery accuracy specification does not match the design verification test criteria. Address the inconsistencies and also verify that all system specifications listed in the instructions for

use are accurate with respect to the CADD-Legacy Model 1400 pump system for infusion of Levodopa-Carbidopa Intestinal Gel.

3. The device operating temperature specification is 2C to 40C. Verify that this is consistent with the acceptable temperature exposure specifications during administration of the drug.

4.  (b) (4)

### **PATIENT INSTRUCTIONS FOR USE (IFU)**

1. We recommend including a statement to administer enteral nutrition through a different port to help prevent blockage of the port used to deliver Duopa.
2. The IFU states that the “Duopa cassette” is used interchangeably with the  (b) (4)  throughout the instructions. To help prevent confusion, we recommend using one consistent term throughout the instructions.
3. The instructions refer to terms, such as  (b) (4) which may not be understood by patients. We recommend revising these terms for more patient friendly language.
4. The IFU states that  (b) (4)  which is inconsistent with the risk analysis submitted with the usability study. Please clarify and justify this statement.
5. We recommend adding a statement that the proposed pump should only be used with approved carbidopa and levodopa enteral suspension cassettes.
6. We recommend removing  (b) (4) as examples of pump screen shots to help prevent confusion. For example, the morning dose pump screen shot shows  (b) (4). We recommend removing  (b) (4) as patients may think this is the dose that needs to be on their screen.

### **HEALTH CARE PROVIDER INSTRUCTIONS FOR USE**

1. As currently proposed, there is conflicting information between the  (b) (4)  and “Legacy 1400 Operator’s Manual”. For example, the  (b) (4) 

(b) (4) but the “Legacy 1400 Operator’s Manual” provides information about how to use the Reservoir Volume feature. In addition, the “Legacy 1400 Operator’s Manual” contains programming information that is not present in the (b) (4) document. We recommend combining the two instructional materials for HCPs into one document, address inconsistent information, and remove instructions associated with features of the pump that you do not intend for HCPs to use. Once you have combined the two instructional materials into one document, assess if there are new critical user tasks that were not evaluated in your previous human factors study. The new critical user tasks that are identified will need to be evaluated in another human factors validation study.

### **PRODUCT DESIGN**

1. You should develop an alarm feature alerting patients when the cassette is empty. This may help prevent dose administration errors from occurring.
2. The morning dose button has to be depressed twice for delivery while the extra dose button only has to be depressed once for delivery. To help prevent morning dose omission errors from occurring, consider designing the pump so the morning dose button only has to be depressed once for delivery. If this is not feasible through product design, consider revising the IFU to improve clarity.
3. The programming of the morning dose has to be done in run mode while all other programming occurs in stop mode. To help prevent confusion during programming, consider revising the pump software so the morning dose can be programmed in stop mode. If this is not feasible through product design, consider making revisions to the IFU to improve clarity.
4. The red cap on the drug cassette fits into the PEG-J tubing. Consider changing the design of the red cap on the drug cassette so that it does not fit into the PEG-J tubing.
5. We recommend deactivating certain features in the pump software that patients or HCPs do not use, such as the Reservoir Volume function.
6. The given value only reports the amount of drug administered since the last clearing of the given value. The pump software does not report breakdown of dosing (i.e., number and amount of extra doses) and it creates more steps for the HCPs during programming. If this feature is unnecessary, consider removing it from the pump. .
7. Consider additional product design changes to address task failures seen in the usability study. If you cannot improve upon task failures seen in the usability study through product design changes, we recommend improving the IFU for clarity. If any product design changes require making changes to the IFU, we recommend conducting a human factors simulated use study prior to approving the redesigned device and revised IFU.

**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>.

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 Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, MD  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

WILLIAM H Dunn  
03/28/2014