

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203952Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22, 2014
From	Gerald D. Podskalny DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203952 Class 2 Resubmission
Supplement#	
Applicant	AbbVie Inc.
Date of Submission	July 11, 2014
PDUFA Goal Date	January 11, 2015
Proprietary Name / Established (USAN) names	Duopa (carbidopa-levodopa suspension)
Dosage forms / Strength	Carbidopa 4.63mg/mL and levodopa 20 mg/mL
Proposed Indication(s)	1. Advanced Parkinson's Disease
Recommended:	<i>Approval</i>

1. Introduction

AbbVie submitted a Class 2 Resubmission for carbidopa-levodopa intestinal suspension(LCIS) sent to FDA on July 11, 2014. The resubmission is in response to the Complete Response action by the FDA for the original 505(b)(2) NDA submitted on March 28, 2014. The Complete Response letter cited deficiencies in product quality, the assessment of device specifications and safety, and deficiencies in human factors testing. The resubmission addresses these deficiencies and additional requests for clarification that were included in the Complete Response letter.

2. Background

The Sponsor's resubmission addressed the deficiencies and requests for clarification described in the Complete Response letter in a point for point fashion.

The disciplines listed in Table 1 evaluated the Sponsor's resubmission. The primary reviewer in each discipline and the recommendation action appear in the second and third columns of Table 1.

Table 1

Review Discipline	Reviewer	Recommendation
Chemistry Manufacturing and Controls Chemistry Review	Charles Jewell, PhD	Approvable
Office of New Drug Quality Assessment Biopharmaceutics Review	Kelly Kitchens, PhD	Approvable
Center for Devices and Radiological Health Reliability and Mechanical Engineering	CDR. Alan Stevens	Approval
Center for Devices and Radiological Health Biomedical Engineer/Human Factors Review	QuynhNhu Nguyen	Acceptable
DMEPA Human Factors and Labeling Review	Jacqueline Sheppard, PharmD	Acceptable

CDER/Division of Neurology Products Medical Review	Leonard P. Kapcala, M.D.	Approval
Office of Medication Error Prevention and Risk Management (Proprietary Name)	Kellie A. Taylor, Pharm.D., MPH	Acceptable

3. CMC/Device

CMC

AbbVie addressed the CMC deficiencies listed in the Complete Response (CR) letter. Additional information was provided in response to the CMC reviewer's information request sent to AbbVie while the application was under review.

CMC Listed Deficiencies in the CR Letter

1. The analytical method for determining the (b) (4) should be adequately described, 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.

CDTL Comment:

During the initial review cycle, the sponsor reported (b) (4). It resulted in non-uniform dispensing of the drug contents in the cassette through the pump delivery system. The Sponsor changed production methods (b) (4).

(b) (4)
(b) (4) Dr. Jewell noted, the sponsor's response is **acceptable**.

AbbVie's response clarified that they would use (b) (4).
(b) (4)
(b) (4)
(b) (4) In his review, Dr. Jewell noted, the sponsor's response is **acceptable**.

2. Provide complete stability data that includes the (b) (4) measurement to cover the 0 weeks, 5 weeks, 10 weeks and 15-week time points for three batches of commercial scale drug product (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, 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.

CDTL Comment:

Dr. Jewell found the stability data provided (on commercial scale batches) in the resubmission and in a subsequent amendment received during resubmission review cycle, supports 12 weeks of refrigerated storage, after a maximum of 24 months of storage . The results of (b) (4) testing and morning dose testing supported his conclusion.

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*).

CDTL Comment:

Dr. Kitchens (Biopharmaceutics reviewer) concluded the dissolution method was deemed acceptable during the last review cycle. The full dissolution profile test results for three commercial scale batches of product support the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 40 minutes using (method) 2 paddle at 25 rpm, in 0.05 M acetate buffer, pH 4.5 at 37°C in 500 mL. Dr. Kitchens concluded these results are **acceptable**.

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.

CDTL Comment:

Stability data was collected from the time the product was moved from frozen to refrigerated storage for three commercial scale batches of Duopa. The Sponsor provided the in two portions, the stability data for 5 and 8 weeks were included in the sponsor resubmission and the data for weeks 10, 12 and 15 were submitted as an amendment. Dr. Kitchens concluded the stability data is **acceptable**.

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) a 10-fold difference. Clarify this discrepancy (b) (4)

CDTL Comment:

Dr. Kitchens stated in her review, AbbVie clarified that the correct value for the slope decreasing levels of [REDACTED] (b) (4). The response did not change information provided in Module 3 of the NDA. The response is **acceptable**.

Additional CMC Issues

1. Change all references from [REDACTED] (b) (4) to "carbidopa and levodopa enteral suspension" in the labeling to comply with the Agency's drug product dosage form naming conventions.

CDTL Comment:

AbbVie changed all of the labeling references within this complete response resubmission in Module 1, Section 1.14.1 have been updated from [REDACTED] (b) (4) to an established name of "carbidopa and levodopa enteral suspension".

2. The comparability protocol to accept [REDACTED] (b) (4) with a reporting category of annual report is not acceptable. This would require prior approval labeling changes.

CDTL Comment:

AbbVie agreed to submit prior approval labeling changes for future changes [REDACTED] (b) (4).

Facilities Inspections

The original manufacturing facilities inspections were completed in March 2014, and that two of the sites were recommended for re-inspection in the Dec. 2014 period. The overall recommendation for the sites for NDA 203952 (DUOPA) will now remain acceptable until 3/31/2015.

CMC Recommendations:

Chemistry Manufacturing and Controls Chemistry Drug Quality=**Approvable**
Office of New Drug Quality Assessment Biopharmaceutics=**Approvable**

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

Reliability and Mechanical Engineering

CDRH's adverse event and recall database search for the CADD Legacy system found the most frequently reported adverse events are leaking of the medication cassette, air bubbles in the cassette, and occluded cassettes. CDRH issued a Class II recall (Z-0876-2008) to address the leaking cassettes that opened in 2007 and ended in 2008. Adverse events related to air bubble formation and occlusion was assessed during the CDRH review of the device safety case.

The CDRH engineering review of the resubmission focused on Infusion Delivery Error hazards. This included under delivery, over delivery, and delay of therapy hazards. The hazard

analysis assumed that patients could detect the return of Parkinson's symptoms due to faulty drug delivery with sufficient time to adjust the dose for improved response.

AbbVie provided additional information to address the deficiencies raised in CDRH's Hazard Analysis related to the potential for delivery of LCIS at the incorrect rate. In each case, the Hazard Analysis did not need to be changed; the deficiencies were addressed using additional information in the requirements and design documents or in the design history file provided in the resubmission.

The Sponsor's resubmission addressed approvability issues described in the Complete Response letter and requests for additional information or clarification (Review Issues). The resubmission included results from additional testing to better characterize the delivery accuracy over a wider operating range. The test conditions were modified to evaluate the effect of changes in the operating temperature range was modified from (b) (4) °C to 2°C, to align with AbbVie's temperature requirements. The continuous flow rate accuracy was evaluated at 0.1ml/hr (minimum continuous programmable rate), 0.4ml/hr (slightly below the minimum clinically relevant flow rate), and 20ml/hr (maximum continuous programmable rate). Corrective action to clarify the range of this specification for the product accompanied this action. The morning dose accuracy was tested to follow the clinical method of delaying 20 minutes after removal of the medication cassette from the refrigerator prior to dosing.

In the CR letter, the CDRH engineering reviewer requested:

1. Additional software documentation for the current release version
2. Documentation of remaining unresolved anomalies,
3. A static analysis report for the current release version.

Additional information needed to complete CDRH's assessment of causes and hazard controls from the device hazard analysis documentation (MAF (b) (4), Amendment 3, VOL 6 TAB 10B CADD-Legacy 1400 Pump Hazard Analysis).

The resubmission materials included the full software revision history (within MAF (b) (4)) with reference to the software validations for the current release version that was presented in a table. AbbVie submitted documentation showing that the unresolved software anomalies do not apply to the U.S. version of the CADD-legacy 1400 Pump.

The static analysis tools used for the CADD-Legacy Duodopa Desk Check included three software components.



Smiths Medical, using their internal R&D Department Procedure (RD028-C) specified the tools for the software analysis and they tested the pump software. Smiths Medical identified eight defects during testing that were corrected as of March 22, 2001. Smiths Medical did not

release new versions of pump software into production prior to resolution, correction, and validation of all alerts and defects in keeping with their operating procedures.

AbbVie provided information to address each potential hazard control deficiency listed in the FDA's CR letter.

Additional CDRH Engineering Review Concerns

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 and time to detection are derived from the design verification tests using LCIS.

AbbVie Response:

AbbVie conducted additional time to occlusion detection testing with the CADD-Legacy Model 1400 pump using LCIS (the original test was conducted using water). Testing was completed for three pumps at 0.4 mL/hr (representative continuous rate) and 40 mL/hr (Morning/Extra Dose pumping rate) using production lot cassettes of LCIS at nominal temperature conditions (approximately 23°C). The Operators Manual (HCP IFU; Section 5) was updated to reflect the results using LCIS. The minimum time to occlusion detection was (b) (4) minutes and (b) (4) seconds at an occlusion pressure of 12 psi and (b) (4) hours (b) (4) minutes and (b) (4) seconds at a minimum pumping rate of 0.4 mL/min at an occlusion pressure of 40 psi. The CDRH reviewer concluded the response adequately characterizes the performance of the occlusion sensing system.

- 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 28 psi.

AbbVie Response:

Based on the test information described above, therapy could be reduced from the prescribed dose for a period lasting from (b) (4) seconds to (b) (4) minutes before a patient receives the alarm indicating that there is a problem with dose delivery. At the lowest tested flow rate, 0.4 mL/hr, the alarm would not activate for (b) (4) minutes, resulting in a potential under delivery of the intended dose up to (b) (4) mg (b) (4) mg/hr). If a patient noticed this reduction in therapy, due to a gradual return of symptoms, over the (b) (4) minutes, the patient is trained to administer an extra dose, if prescribed. The increased delivery rate for the extra dose (40mL/hr) would trip the occlusion alarm within (b) (4) seconds (Table 9), alerting the patient to a problem.

CDRH Reviewer Comments: The response adequately characterizes the performance of the occlusion sensing system.

CDTL Comment:

It is reasonable to assume that a patient would notice a change in clinical response if jejunal delivery of Duopa were decreased by partial occlusion in the connection pathway. AbbVie's response assumes that the cause of occlusion is corrected (or correctable) and that the bolus dose could be delivered as prescribed. The medication guide also advises patients to carry at oral carbidopa-levodopa at all times to provide a safeguard against the return of PD symptoms if the pump should fail.

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 (b) (4) 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 Solution.

AbbVie Response:

Earlier information in MAF- (b) (4), e.g., occlusion alarm time for (b) (4) infusion rate the information was not specific to the CADD-Legacy Model 1400 for use with LCIS. The specification for a maximum infusion rate of 20 mL/hr in the Operators Manual (HCP IFU) is accurate with respect to CADD-Legacy Model 1400 pump system for Duopa and reflects the results of testing using LCIS. Data to support specifications are in Appendix A and in MAF- (b) (4), Amendment 5 (DVT-1258R Rev. 002 and ETR-342). **CDRH Reviewer Comments: the response is acceptable.**

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

AbbVie Response:

There is no temperature exposure specification during administration of LCIS, the IFU's reflect the device operating temperature specification of 2°C to 40°C, which encompasses the expected patient use environment. Data to support specifications are in Appendix A and in MAF- (b) (4), Amendment 5. **CDRH Reviewer Comments: the response is adequate.**

4.  (b) (4)

(b) (4)

AbbVie Response:

As stated in the Safety Assurance Case for the CADD-Legacy 1400 pump, the Air Detector is not required for enteral delivery. (b) (4)

(b) (4) the updates made for the CADD-Legacy 1400 pump so the feature was disabled (hard coded) in the software, and the screen was removed from the user interface. (b) (4)

CDRH Reviewer Comments: the response is adequate.

Recommended Action CDRH Reliability and Mechanical Engineering

All CR deficiencies related to the infusion device have been adequately addressed. The final recommendation action for this application is for **Approval**.

CDRH Human Factors Review

The review of the original human factors (HF) study results in the NDA found several failures in the patient and in the healthcare providers (HCP) groups. There were also deficiencies in the patients and HCP manuals. It was determined that another HF study was needed to address task failures observed in patients and healthcare providers performing critical tasks during the original HF testing

“...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.”

The sponsor submitted the results of a supplemental simulated-use validation test that was conducted with 15 participants that included 9 Duopa naïve Healthcare Providers and 6 Duopa naïve patients. All participants received training and returned 1 day after to perform the supplemental testing.

Quynh Nhu Nguyen, Combination Products Human Factors Specialist in CDRH reviewed the supplemental HF study. The supplemental human factors (HF) study was considered complementary to the original HF study to validate the product modifications implemented after the original HF study.

These modifications included (From the CDRH HF review)

- Revised patient instructions for use (Patient IFU)
- Revised healthcare provider instructions for use (HCP IFU)
- Revised user training that more accurately mimics the patient-HCP interactions and the naïve

Healthcare Provider Duopa trainer interactions in clinical practice (From the CDRH HF review)

- Educational and support materials, including

- Educational and support materials, including
- Educational materials based on the IFU
- Duopa patient videos
- Helpline available to patients and HCPs

The results showed one failure in the patient group. This participant was unsuccessful during their first attempt to adjust the Morning Dose. The patient delivered the previously programmed Morning Dose instead of the adjusted dose Morning Dose selected for the exercise. After participant recognized something was not right, the participant appropriately stated they would call the helpline for assistance. After a delay, the scenario was repeated and the participant successfully completed the task of adjusting the morning dose.

AbbVie plans to provide training and support services for the use of Duopa to patient and physician, they reported that a patient and physician support program will be available upon approval. These services will be offered through a centralized program and upon enrollment, each patient will be assigned a dedicated Nurse Case Manager who has received extensive training on use of the Duopa system. The Nurse Case Manager will coordinate in-home personalized training delivered by registered nurses that is scheduled around a patient's planned treatment

CDRH Human Factors Recommendation:

This human factors reviewer found Abbvie's response to the HF deficiencies outlined in the Complete Response Letter and the results of the supplemental HF study within this NDA resubmission acceptable. All of the deficiencies have been adequately addressed, and the supplemental human factors validation study results demonstrated that the modifications to the patient and healthcare provider Instructions for Use and training program have effectively improved the ability of users to use the product.

CDTL Comment:

The conclusions by CDRH are support a decision to approve the application.

PATIENTINSTRUCTIONSFORUSE(IFU)

Quynh Nhu Nguyen, Combination Products Human Factors Specialist in CDRH reviewed AbbVie's response to the additional concerns raised in the CR letter (listed below). CDRH concluded that AbbVie's response to these additional comments and recommendations were adequate.

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.

Summary of AbbVie's Response:

AbbVie revised the statement in the Patient IFU to address FDA's comment as follows:

[REDACTED] (b) (4)

2. The IFU states that the “Duopa cassette” is used interchangeably with the [REDACTED] (b) (4) [REDACTED] throughout the instructions. To help prevent confusion, we recommend using one consistent term throughout the instructions.

Summary of AbbVie’s Response:

AbbVie reviewed the product labeling and made revisions to use consistent terminology for the medication cassette reservoir. The term used consistently is "Duopa cassette."

3. The instructions refer to terms, such as [REDACTED] (b) (4) which may not be understood by patients. We recommend revising these terms for more patient friendly language.

Summary of AbbVie’s Response:

The instruction to "Use only extension sets [REDACTED] (b) (4), pay [REDACTED] (b) (4) attention to all warnings and cautions associated with their use." provides specific direction for the extension sets to be used with Duopa. The second part of the comment [REDACTED] (b) (4) is not applicable to the products that are recommended for use with Duopa in the U.S. PI and it has been removed from the Patient IFU.

4. The IFU states that [REDACTED] (b) (4) [REDACTED], which is inconsistent with the risk analysis submitted with the usability study. Please clarify and justify this statement.

Summary of AbbVie’s Response:

The warning statement has been modified to a phrase more applicable to use of the pump with Duopa, "Failure to follow the Warnings and Cautions below could result in return of symptoms, damage to the pump, serious injury, or death in extreme cases."

5. We recommend adding a statement that the proposed pump should only be used with approved carbidopa and levodopa enteral suspension cassettes.

Summary of AbbVie’s Response:

[REDACTED] (b) (4)

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.

Summary of AbbVie's Response:

AbbVie has removed (b) (4), shown on example screen displays to prevent confusion.

HEALTHCARE PROVIDER (HCP) 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) 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.

Summary of AbbVie's Response:

AbbVie has combined the two instructional materials for HCPs into one document to address inconsistent information and they removed or annotated instructions associated with features of the pump that are not recommended for HCPs to use with Duopa. This document was included in the supplemental HF study. No new critical user tasks have been identified or created when the two instructional materials were combined into a single document.

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.

Summary of AbbVie's Response:

AbbVie did not implement the recommended change, they argue that very few patients will use more than a single cassette in a day, *"In the clinical trials, the majority of patients used a single cassette. In the limited number of patients who use more than 1 cassette (> 2000 mg), patients are instructed by their physician to change the cassette at the same time every day so they can appropriately plan their activities without treatment interruption."*

This is consistent with FDA's recommendation to state in the label that the maximum recommended dose is one cassette or less. AbbVie stated in their reply that based on FDA feedback AbbVie would take the suggestion to evaluate the pump alarm features into our lifecycle management planning.

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.

Summary of AbbVie's Response:

The duplication of pressing the morning dose button is a safety feature reducing the risk of accidental delivery. The first press of the MORNING DOSE displays the currently programmed value for confirmation of the intended dose. The second press delivers the morning dose.

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.

Summary of AbbVie's Response:

To address the above issue, this information in the HCP IFU was reorganized by changing (b) (4) to a step in the task flow to improve HCP comprehension. Step 1 now reads, "1. The pump must be running with a cassette attached and in LL0 or LL1. Start the pump, if necessary and confirm the lock level settings." This emphasizes that the pump must be in run mode.

The supplemental HF study demonstrated that the use of the improved IFUs, training, and educational materials, participants (patients and HCPs) were able to complete the tasks necessary to use the Duopa administration system successfully.

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.

Summary of AbbVie's Response:

Based upon the supplemental HF study, the current IFUs with supportive training adequately address removal of the red cap. However, AbbVie is in the process of evaluating the design of the red cap as part of our life cycle management planning.

5. We recommend deactivating certain features in the pump software that patients or HCPs do not use, such as the Reservoir Volume function.

Summary of AbbVie's Response:

The default setting for Reservoir Volume is Not in Use. Programming a reservoir volume value is not required for general use, but is available at provider discretion." In order for the patient to see the Reservoir Volume, the HCP would need to turn it on, which is an activity that the HCP is not instructed to perform. The HCP must activate the function in order for the function to be visible to the patient.

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.

Summary of AbbVie's Response:

The "given value" function is utilized by Smiths Medical and AbbVie during complaint investigations, but is not necessary for use by patients or HCPs with the administration of Duopa.

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.

Summary of AbbVie's Response:

AbbVie has evaluated the task failures in the original HF report along with their root causes and determined that no design changes are required. They determined that the training was more reflective of clinical use (number of sessions and duration) and revisions to the Patient and HCP IFUs to improve usability as suggested by FDA were appropriate actions to mitigate residual risks

The supplemental HF study demonstrated that with the improved IFUs, training, and educational materials, participants (patients and HCPs) were able to successfully complete the tasks necessary to use the Duopa administration system safely and effectively.

Division of Medication Error Prevention and Analysis (DMEPA) Human Factors Review

The DMEPA reviewer also concluded that the Sponsor's resubmission including the results of the supplemental HF study were acceptable.

DMEPA's Recommendations:

The results of the summative human factors study supports the safe and effective use of Duopa by intended end users. We believe that risks have been mitigated to an acceptable level. The DMEPA review team suggested changing the presentation of the strengths of the two components of Duopa (carbidopa and levodopa) from [REDACTED]^{(b) (4)} to “4.63 mg/20 mg per mL”. The Clinical and CMC review teams agree with DMEPA’s proposed change in the presentation of the strengths of the two drug components of Duopa. The presentation in the label and labeling will be changed to “4.63mg /20mg per mL”.

DMEPA’s “Recommendations to the Division” for changes to the Prescribing information and Medication Guide were incorporated into these documents as tracked changes that will be returned to the Sponsor for review.

6. Nonclinical Pharmacology/Toxicology

The submission did not include additional Nonclinical information.

7. Clinical Pharmacology/Biopharmaceutics

The submission did not include additional Biopharmaceutics information.

8. Clinical Microbiology

The submission did not include additional Microbiology information.

9. Clinical/Statistical- Efficacy

The submission did not include additional clinical efficacy information or statistical analyses of clinical efficacy data. Evidence of effectiveness was provided by the results of a single pivotal study reviewed during the first review cycle. Identical studies S187-3-001 and S187-3-002 were combined into a single study under a revised protocol because of difficulty recruiting patients into the separate studies. The results of the pivotal efficacy study results showed that carbidopa levodopa intestinal suspension (Duopa) was superior to oral carbidopa levodopa ($p=0.0015$) and this difference is considered to be clinically meaningful. The results of this single study were sufficiently robust and served as the basis for determining efficacy along with the Agency’s previous finding of safety and effectiveness for carbidopa and levodopa.

10. Safety

The data cutoff date for the original NDA was May 4, 2012. The cutoff date for the 120-Day Update (SU-1) was May 31, 2013 and the cutoff date for the second safety cutoff date from the submission for SU-1 to the resubmission of the NDA (SU-2) was March 31, 2014. At the time of the data cutoff date for the SU-1, two Investigational New Drug (IND) studies and one non-IND study were ongoing. Two additional non-IND studies started enrollment (after the SU-1 submission). In the integrated analysis sets for the United States (US) registration program, no new subjects have been exposed to LCIS, but 203 subjects who were already treated with

LCIS have had additional exposure time in ongoing Study S187-3-005 (enrolled patients from open-label extension of Study S187-3-003 and open-label safety Study S187-3-004 in countries where LCIS is not commercially available). SU-2 contains detailed information for the 203 patients with additional exposure time in the open label, IND studies. A patient discontinued study participation before the data cutoff for SU-1 but this was not reported until after database lock therefore, this patient was excluded from SU-2. Another patient was included in SU-2 even though the patient was reported as discontinued in SU-1 because his or her final study visit did not occur until after the cutoff for the SU-1 update. Data from 17 subjects enrolled in IND Study M12-920 as of the March 31, 2014, data cutoff date are included in SU-2. Data from six patients enrolled in two non-IND studies are also included in SU-2.

Long-Term Exposure

In the US registration program, 351 subjects have been exposed to LCIS for at least 6 months (180 days), including 338 subjects exposed for at least 1 year, 233 subjects for at least 2 years, 162 subjects for at least 3 years, and 68 subjects for at least 4 years

Duration of LCIS Exposure (All LCIS Analysis Set)

Duration Interval ^a	Low Dose		High Dose		All	
	SU-1 N = 159	SU-2 N = 159	SU-1 N = 257	SU-2 N = 257	SU-1 N = 416	SU-2 N = 416
By Number of Days,^b n (%)						
1 to 14	25 (15.7)	25 (15.7)	8 (3.1)	8 (3.1)	33 (7.9)	33 (7.9)
15 to 29	1 (0.6)	1 (0.6)	5 (1.9)	5 (1.9)	6 (1.4)	6 (1.4)
30 to 59	3 (1.9)	3 (1.9)	4 (1.6)	4 (1.6)	7 (1.7)	7 (1.7)
60 to 89	6 (3.8)	6 (3.8)	3 (1.2)	3 (1.2)	9 (2.2)	9 (2.2)
90 to 179	4 (2.5)	4 (2.5)	6 (2.3)	6 (2.3)	10 (2.4)	10 (2.4)
180 to 364	2 (1.3)	2 (1.3)	11 (4.3)	11 (4.3)	13 (3.1)	13 (3.1)
365 to 539	25 (15.7)	25 (15.7)	61 (23.7)	61 (23.7)	86 (20.7)	86 (20.7)
540 to 729	19 (11.9)	7 (4.4)	26 (10.1)	12 (4.7)	45 (10.8)	19 (4.6)
730 to 899	21 (13.2)	6 (3.8)	33 (12.8)	15 (5.8)	54 (13.0)	21 (5.0)
900 to 1094	21 (13.2)	24 (15.1)	37 (14.4)	26 (10.1)	58 (13.9)	50 (12.0)
≥ 1095	32 (20.1)	N/A	63 (24.5)	N/A	95 (22.8)	N/A
1095 to 1259	N/A	10 (6.3)	N/A	25 (9.7)	N/A	35 (8.4)
1260 to 1459	N/A	22 (13.8)	N/A	37 (14.4)	N/A	59 (14.2)
≥ 1460	N/A	24 (15.1)	N/A	44 (17.1)	N/A	68 (16.3)
By Number of Months,^c n (%)						
≥ 6 months (≥ 180 days)	120 (75.5)	120 (75.5)	231 (89.9)	231 (89.9)	351 (84.4)	351 (84.4)
≥ 1 year (≥ 365 days)	118 (74.2)	118 (74.2)	220 (85.6)	220 (85.6)	338 (81.3)	338 (81.3)
≥ 18 months (≥ 540 days)	93 (58.5)	93 (58.5)	159 (61.9)	159 (61.9)	252 (60.6)	252 (60.6)
≥ 24 months (≥ 730 days)	74 (46.5)	86 (54.1)	133 (51.8)	147 (57.2)	207 (49.8)	233 (56.0)
≥ 30 months (≥ 900 days)	53 (33.3)	80 (50.3)	100 (38.9)	132 (51.4)	153 (36.8)	212 (51.0)
≥ 3 years (≥ 1095 days)	N/A	56 (35.2)	N/A	106 (41.2)	N/A	162 (38.9)
≥ 42 months (≥ 1260 days)	N/A	46 (28.9)	N/A	81 (31.5)	N/A	127 (30.5)
Summary Statistics						
Mean ± SD, days	655.2 ± 465.51	793.8 ± 588.13	749.7 ± 438.23	889.8 ± 553.05	713.6 ± 450.65	853.1 ± 567.94
Median (min – max), days	710 (1 – 1611)	910 (1 – 1915)	752 (3 – 1676)	932 (3 – 1980)	721 (1 – 1676)	915 (1 – 1980)
Total patient years	285.2	345.5	527.5	626.1	812.7	971.6

LCIG = levodopa-carbidopa intestinal gel; max = maximum; min = minimum; N/A = not applicable; SD = standard deviation; SU-1 = Safety Update 1; SU-2 = Safety Update 2

Seven patients died due to TEAEs (6 low dose, 1 high dose) since the SU-1, resulting in a total of 34 (8.3% [34/412]) deaths due to TEAEs in Open-Label studies. There were 13 deaths in the low dose LCIS group compared to 21 in the High Dose group.

Discontinuations:

All of the discontinuations (N=7) since the submission of SU-1 were due to death.

Dr. Kapcala found a small number of additional patients with serious, adverse reactions (fatal events included) in SU-2. Forty-three of the 203 patients with additional follow-up time since SU-1 had at least one additional serious adverse reaction in SU-2. The percentage of patients (~21%) of new serious adverse reactions reported by the 203 patients was similar in the high (n=125) and low (n=78) dose groups. The additional serious events were scattered over a wide number of Preferred Terms, adding another one or two patients to the total for each Preferred Term. Dr. Kapcala reviewed the frequency of common (nonserious) adverse reactions and he concluded that the frequency of these adverse reactions did not change significantly with the

additional information in SU-2. The sponsor conducted broad and narrow SMQ analyses of the PTs and these analyses were very similar to the results reported in the original ISS and SU-1.

CDTL Comment:

I concur with Dr. Kapcala's conclusion that the safety profile of Duopa is not changed by the information presented in the most recent safety update (SU-2). The safety of procedure related adverse reactions and treatment associated adverse reactions appears to be reasonable in this population of patients advanced (greater than 10 years) Parkinson's disease. Alternative treatments such as a deep brain stimulation would also require patients accept additional risks compared to simply taking oral medications.

11. Advisory Committee Meeting

An Advisory Committee was not held for this application.

12. Pediatrics

Pediatric studies under PREA are not required for this Orphan designated product. This product was granted orphan designation under the proprietary name Duodopa on January 18, 2000, for the "Treatment of late stage Parkinson's disease".

13. Other Relevant Regulatory Issues

There were no new regulatory concerns identified during our review of the Sponsor's resubmission.

- Application Integrity Policy (AIP), **None identified during the initial review.**
- financial disclosures, **Acceptable**
- other GCP issues, **None identified during the initial review.**
- DSI audits, **No concerns identified during the initial review.**
- **Gastroenterology consult**

The Division requested Gastroenterology provide a consultative review of the procedure related (PEG-J) adverse reactions during the first review cycle. The frequency and type of adverse reactions associated with PEG-J tube insertion in the Duopa development was similar to the events reported in patients who have similar tubes inserted for other reasons.

14. Labeling

Proprietary name review

The Office of Medication Error Prevention and Risk Management sent a letter to the Sponsor on October 30, 2014, stating the proprietary name is acceptable.

Physician Labeling

The Division added a subsection in Warnings and Precautions describing the risk for neuropathy. The pathogenesis of neuropathy in patients with PD, and its association with LCIS not fully understood. It is not clear that vitamin deficiency or the presence of comorbid conditions increase the risk for neuropathy. In addition, recently published case reports describe neuropathy in patients with PD taking oral carbidopa-levodopa products. Symptomatic neuropathy was reported in patients enrolled in the LCIS clinical trial program and in postmarketing cases. Neuropathy did not consistently improve with vitamin supplements (B6, B12, and folate) or by discontinuing by LCIS. We recommend clinical monitoring for neuropathy in all patients taking LCIS and electrodiagnostic testing if needed. Although, it seems logical that patients with preexisting conditions that cause neuropathy are at greater risk for neuropathy associated with LCIS, there is insufficient evidence to support this conclusion at this time.

Hydrazine is a degradation product of carbidopa and it is a known animal carcinogen. Carbidopa degrades faster in LCIS compared to oral carbidopa containing products increasing exposure to hydrazine. However, evidence showing hydrazine is associated with an increased risk for cancer in humans is lacking. In theory, the potential risks associated with high levels of hydrazine are worrisome but it does not preclude approval in patients with advanced PD with limited treatment options. However, patients with less advanced PD should not be encouraged to use LCIS. The recommended dose of LCIS should be one cassette (500 mg of the carbidopa component) per day. We note that the LCIS prescribing information approved by Health Canada and the EMA describe the genotoxic and “carcinogenic” potential in the Warnings section but the statement continues, and acknowledge the clinical significance of the nonclinical finding is unknown. In essence, the statement refers to nonclinical findings and acknowledges that the absence of clinical data supporting an increased risk for cancer in patients taking LCIS. We decided to describe the nonclinical findings in the appropriate sections of the label. Because there is no clear signal for an increased risk for cancer associated with this product, we have decided against including this information in Warnings and Precautions, if the nonclinical findings have unknown clinical meaning.

Address important issues raised by OSE Divisions.

Carton and immediate container labels (if problems are noted)

The Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM) completed their review of the product label, related Medication Guide, Patient Instructions for Use (IFU) and Healthcare Provider (HCP) IFU.

DMEPA’s comments and recommendations for the Product Label and Medication Guide were incorporated into the edited label sent to the sponsor for their review and feedback. For the most part, the Division accepted DMEPA’s recommendations. Recommendations from Patient Labeling and DMEPA for changes to the Patient and HCP IFUs were incorporated in the version sent to AbbVie with minor edits from the Division.

DMEPA’s recommendations for labeling were sent to AbbVie (below)

A. Carton Labeling

1. Place a “discard after” or “use by” date on the principal display panel (PDP) of the carton labeling to minimize the risk of using deteriorated drug product.
2. Relocate the storage statement from the side panel to appear on the PDP (“Store in the refrigerator between 2°-8°C.”) to alert patients/caregivers of the need for refrigeration until use. To the side panel, add an additional statement similar to “Pharmacists: Store frozen. Thaw in refrigerator immediately prior to dispensing.” as special instructions for dispensing pharmacist.
3. Express the net quantity as volume [REDACTED] ^{(b) (4)} as the dosing calculation provided in Section 2 are provided in volume (e.g., 100 ml [REDACTED] ^{(b) (4)}). This will allow for uniformity between the prescribing information and the label.
4. Ensure the proprietary name, established name, and strength are the most prominent information on the Principal Display Panel.

B. Container Label

1. Increase the prominence of the storage requirements by using either bolded letters or larger font size. This will alert dispensing pharmacy pharmacies and patients to the unique storage requirements of the product.
2. Add a statement similar to “Use product at room temperature” to mitigate the risk of missed dose related to pump failure due to clogged product.
3. Express the net quantity as volume [REDACTED] ^{(b) (4)} as the dosing information provided in Section 2 is provided in volume, as is the statement of strength (expressed per mL). This will allow for consistency between the prescribing information and the label.
4. Ensure the proprietary name, established name, and strength are the most prominent information on the Principal Display Panel.



15. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action Approval

Risk Benefit Assessment

The benefit to patient with advanced PD who are experiencing significant daily off time appears to be substantial. The pivotal efficacy study results show robust p-values with internal consistency across most of the secondary endpoints. The potential risk associated with increased levels of hydrazine as a potential human carcinogen remains a safety concern however; this risk is considered in a population with a long duration of PD who have substantial disability with limited treatment options.

The Sponsor proposed a REMS with an ETASU (elements to assure safe use) that included

 (b) (4)

. After considering all of the safety information in the application, I do not find that LCIS poses a unique risk to patients with advanced PD compared to marketed oral carbidopa levodopa products. The PEG-J procedure does not poses an increased risk for adverse reactions that is greater than the risk associated with feeding tube insertion. The theoretical but unobserved risk associated with higher exposure to hydrazine is justifiable in this very advanced group of patients with limited treatment options. The majority of patients in the clinical development program used a maximum of one cassette of LCIS per day. The major portion of the clinical safety experience, including exposure to hydrazine, also falls below one cassette per day dose of LCIS. This experience supports a recommendation that the label should indicate that the maximum recommended dose should be one cassette per day. The available information does not indicate that at REMS would improve the safe use of LCIS, with or without an ETASU.

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Division of Neurology Products

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

/s/

GERALD D PODSKALNY
12/22/2014