# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203952Orig1s000

# <u>OTHER REVIEW(S)</u>

# MEMORANDUM

**REVIEW OF REVISED LABEL AND LABELING**

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| **Date of This Memorandum:** | January 6, 2015 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | NDA 203952 |
| **Product Name and Strength:** | Duopa (Carbidopa and Levodopa) Enteral Suspension, 4.63mg/20 mg per ml |
| **Submission Date:** | December 22, 2014 |
| **Applicant/Sponsor Name:** | Abbvie Pharmaceuticals |
| **OSE RCM #:** | 2014-1748-01 |
| **DMEPA Primary Reviewer:** | Jacqueline Sheppard, PharmD |
| **DMEPA Acting Team Leader:** | Vicky Borders-Hemphill, PharmD |

## 1 PURPOSE OF MEMO

Division of Neurology Products (DNP) requested that we review the revised container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

## 2 CONCLUSIONS

The revised container label and carton labeling is acceptable from a medication error perspective.

[1] Sheppard J. Label and Human Factors Review for Duopa (NDA 203952). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 12. 18 p. OSE RCM No.: 2014-1748.



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Reference ID: 3683107

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

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/s/

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JACQUELINE E SHEPPARD
01/06/2015

BRENDA V BORDERS-HEMPHILL
01/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

**Date:** December 3, 2014

**From:** CDR Alan Stevens, Reliability and Mechanical Engineering
OMPT/CDRH/ODE/DAGRID/GHDB

**To:** Dr. Tracy Peters, Senior Regulatory Health Project Manager
OMPT/CDER/OND/ODEI/DNP

and

Dr. Gerald Podskalny, Clinical Team Leader
OMPT/CDER/OND/ODEI/DNP

**Subject:** CDRH Consult for NDA 203952, infusion pump for enteral delivery of Levodopa / Carbidopa Intestinal Gel

Drug Applicant: AbbVie
Device Sponsor: Smiths Medical
Device Name: CADD Legacy 1400 Pump System

**Recommendation: Approve**

# I. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203952. The device constituent of this combination product consists of an infusion pump system.

**Review Summary**
I have conducted a review of the applicant's CR letter response. I find that all responses are acceptable and have no further deficiencies to communicate.

The CR deficiencies identified in my February 2014 review included unresolved software anomalies, inconsistencies in system specifications, missing delivery accuracy data, and unexplained hazard mitigations to prevent Duopa overdose.

The applicant's responses to these deficiencies are thorough and complete.

# II. Documents

Additional information is included within the complete response resubmission to FDA's March 28, 2014, CR Letter.

Documentation for the infusion pump is also contained in device master file, MAF (b) (4)

# III. Review

Indications for Use

| Product | Indications for Use |
|---|---|
| CADD 1400 Legacy Pump System | The CADD-Legacy 1400 Pump is indicated solely for enteral delivery of medication contained in a medication cassette reservoir supplied by AbbVie. The medication cassette reservoir attaches to the bottom of the pump. |
| Levodopa / Carbidopa Intestinal Gel | Levodopa-carbidopa intestinal gel is a combination of levodopa and carbidopa, indicated for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4) |

Device Description

The CADD-Legacy 1400 Pump System (hereinafter referred to as "CADD-Legacy" or "the pump") is a modification to the existing FDA Cleared CADD-Legacy PCA Pump System (K982839) and Medication Cassette Reservoir (K846772). The CADD-Legacy 1400 Pump System was developed as a specific enteral medication system and will not be indicated for enteral feeding applications. Prior to launching the CADD-Legacy 1400 Pump System, changes were made to the CADD-Legacy PCA System (b) (4) as described in TAB 7 of MAF (b) (4), Amendment 3), labeling, and software to modify features and capabilities that address the needs for enteral delivery of medication. The CADD-Legacy 1400 Pump is supplied with the following accessories:

- Remote Dose Cord
- Pump Pouch
- Protective Cassette
- Battery Door

All four accessories have been cleared in other 510(k) submissions. Refer to Table 3-1 below for the matrix of accessories and associated 510(k)s.

**Table 3-1.** List of CADD-Legacy® 1400 Pump accessories and Cleared 510(k)s.

| Description | Product Code(s) | 510(k) |
|---|---|---|
| CADD-Legacy® Remote Dose Cord | 21-6220 | K982839 |
| CADD-Legacy® Pump Pouch, Single Use, 50/100 mL, 10-pack | 21-2170[1] | K982839 |
| CADD-Legacy® Battery Door | 21-6216 | K982839 |
| Pump Admin Set Housing, Protector | 21-6235 | K982839 |

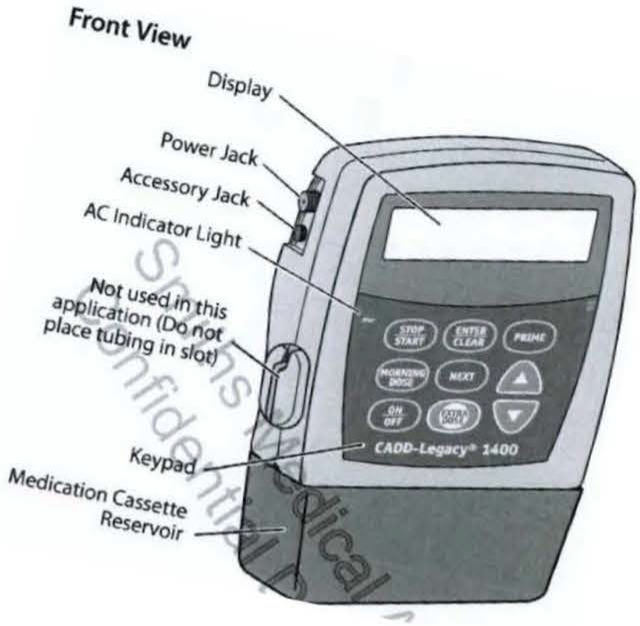
The CADD-Legacy 1400 Pump will be used with a custom enteral Medication Cassette Reservoir and the CADD-Legacy 1400 Pump will be supplied non-sterile. A red warning flag has been added to the extension tube to warn against intravenous connection of the Medication Cassette Reservoir. This Medication Cassette Reservoir, product code 21-7110, has not been part of a 510(k) submission. It is the subject of Drug Master File DMF- (b) (4)

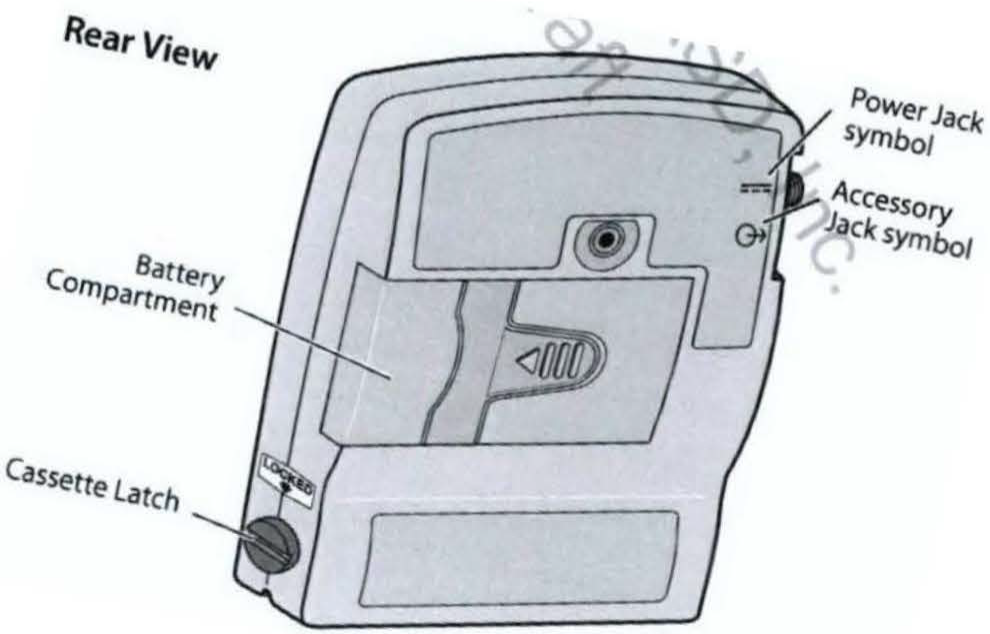
While the CADD-Legacy® 1400 Pump may be used in the hospital, its primary intended use is in the alternate site environment - including but not exclusive to treatment of patients in their homes, institutional care centers, or physician offices.

The CADD-Legacy 1400 Pump consists of the following major components: user interface, sensors, power port, structural components, electronics, pumping mechanism, watchdog timer, pump battery and circuitry, real time clock (RTC), on-board memory, and accessories.

User Interface
A picture of the device user interface is provided below and the table includes a brief description for the function of each key.

| Name of Key | Description of Use |
|---|---|
| STOP/START | The STOP/START key is used to transition the pump from the STOP mode to the RUN mode or form the RUN mode to the STOP mode. Additionally, pressing this key will acknowledge and cancel some alarms. Pressing the STOP/START key triggers this function. |
| ENTER/CLEAR | The ENTER/CLEAR key is used to save an edited value or clear the value of a variable associated with the currently displayed screen. Pressing the ENTER/CLEAR key triggers this function. |
| PRIME | The PRIME key is used to deliver a controlled amount of fluid during STOP mode in order to help remove air from the disposable reservoir and tubing. Pressing the PRIME key triggers this function. |
| NEXT | The NEXT key will generally be used for navigation between screens and to acknowledge alarms. Additionally, pressing this key will both acknowledge and cancel the alarm. Pressing the NEXT key triggers this function. |
| UP ARROW | The Up Arrow key is used to increase the value of a variable associated with the currently displayed screen when in EDIT mode. Pressing the Up Arrow key triggers this function. |
| DOWN ARROW | The Down Arrow key is used to decrease the value of a variable associated with the currently displayed screen when in EDIT mode. Pressing the Down Arrow key triggers this function. |
| ON/OFF | The ON/OFF key is used to put the pump into a low power state when not in use. Pressing the ON/OFF key triggers this function. |
| EXTRA DOSE | The EXTRA DOSE key is used to implement the demand (or "extra") dose feature. When this key is pressed in the RUN Mode, the pump initiates processing for the extra dose. |
| MORNING DOSE | The MORNING DOSE key is used to implement the loading bolus (or "morning dose") feature. When this key is pressed in the RUN Mode, the pump initiates processing for the morning dose. |
| Remote Dose Cord | The Remote Dose Cord is used to remotely implement the morning dose and extra dose features. When the button on the Remote Dose Cord is pressed while the CADD-Legacy® 1400 Pump is in RUN Mode, the pump initiates processing for the morning dose or extra dose. |


Front View
Display
Power Jack
Accessory Jack
AC Indicator Light
Not used in this application (Do not place tubing in slot)
Keypad
Medication Cassette Reservoir
STOP START
ENTER CLEAR
PRIME
NEXT
ON OFF
CADD-Legacy® 1400


Rear View
Power Jack symbol
Accessory Jack symbol
Battery Compartment
Cassette Latch
LOCKED

Sensors
The infusion pump includes three sensors in the design for detecting hazardous situations. The sensor name and a description of its purpose are identified in the following table:

| Sensor Name | Description of Use |
|---|---|
| Upstream Occlusion Sensor | Detects upstream occlusions in the infusion line of the Medication Cassette Reservoir prior to reaching the pumping mechanism. |
| Downstream Occlusion Sensor | Detects downstream occlusions in the infusion line, which occur downstream of the pumping mechanism. |
| Medication Cassette Reservoir Detection Sensor | Detects if there is a Medication Cassette Reservoir properly attached |

Structural Components
The main structure for the CADD-Legacy' 1400 Pump consists of a front and rear housing enclosing the microprocessor and printed circuit board, display and pumping mechanism; battery compartment and a cassette latch assembly.

Electronics
The CADD-Legacy" 1400 Pump contains a microprocessor and other circuitry which control the CADD-Legacy' 1400 Pump. The microprocessor and circuitry are located on a printed circuit board. The board contains the Central Processing Unit (CPU), motor driver circuitry, and other circuitry. The circuitry is designed to reduce the susceptibility to interference from electromagnetic fields and to dissipate electrostatic discharge.

Pumping Mechanism

The pumping mechanism of the CADD-Legacy 1400 Pump is [redacted] (b) (4)

Pumping Mechanism Sequence

[redacted] (b) (4)

[redacted].

[redacted] (b) (4)

Power Requirements

Power for the CADD-Legacy® 1400 Pump is supplied by two "AA" alkaline batteries. The CADD-Legacy 1400 Pump has been designed to accommodate two (2) batteries that mechanically conform to NEDA/ANSI standard 15A or IEC LR6 (type "AA"). This is identical to the CADD-Legacy PCA Pump. The CADD-Legacy 1400 Pump is also capable of being powered with an AC adapter, although an AC adapter is not being supported for the CADD-Legacy 1400 Pump.

The expected life of two (2) "AA" batteries is 100 hours at 100 ml/16 hours, or approximately fourteen (14) days at ten (10) ml/day (nominal). This estimate is based on laboratory tests conducted at room temperature using two (2) new batteries. Actual battery life will vary depending on the brand of battery, battery shelf life, temperature conditions, and delivery rate. An internal battery powers the clock. The internal battery has an expected life of five (5) years and is replaced by Smiths Medical.

Operational Specifications and Descriptions

| Characteristic | Specification |
|---|---|
| System Infusion Delivery Accuracy | |

<table>
<tr><td></td><td>

**Table 3. System Delivery Accuracy (LCIG)**

| | |
|---|---|
| Therapy[a] | ±10% |
| Continuous Rate[b] | ±10% @ flow rates between 0.4 mL/hr to 20 mL/hr |
| Extra Dose[b] | ±10% |
| Morning Dose[b,c] | ±10% |
| Accessories | 100 mL medication cassette reservoir with 36" 0.10" I.D. tube |

a. Therapy delivery accuracy: program to deliver a 10 mL morning dose with a 5 mL/hr continuous rate and three 3 mL extra doses, with a total of 100 mL of medication delivered. Pumps were evaluated in latch down, upside down, and horizontal position. The medication cassette with Duopa (carbidopa and levodopa enteral suspension) initially is cold (approx. 2°C). Remove cassette from the refrigerator, wait 20 minutes, and then conduct the test at nominal temperature.

b. At nominal temperature (23°C ± 5°C)

c. An additional –4% change may be seen for the morning dose when cassette starting temperature is 2°C and placed at room temperature (23°C ± 5°C) for 20 minutes prior to use.

In addition to the above specifications, the following warning is included in the Operator's Manual (HCP IFU).

WARNING: System delivery inaccuracies beyond the stated accuracy may occur as a result of back pressure or fluid resistance, which depends upon temperature, medication viscosity, catheter size, extension set tubing, flow rates, and orientation of the pump system.

</td></tr>
<tr><td>Flow Rates</td><td>0.4mL/hr to 20 mL/hr<br>It can be set in 0.1 mL/hr increments.</td></tr>
<tr><td>Size</td><td>4.1cm x 9.5cm x 11.2cm, excluding cassette</td></tr>
<tr><td>Weight</td><td>392 gram, including 2 AA batteries and empty 100 mL CADD medication cassette reservoir.</td></tr>
<tr><td>Fluid Ingress Protection</td><td>Splashproof (IPX4)</td></tr>
<tr><td>Pump Alarms</td><td>Low battery<br>Depleted battery<br>Battery dislodged<br>Pump stopped<br>Pump fault<br>Low reservoir volume<br>High delivery pressure<br>Air in line<br>Disposable not attached when run attempted<br>Motor locked<br>Upstream occlusion<br>Downstream occlusion<br>Reservoir volume empty<br>Program incomplete<br>Remote dose cord removed<br>Key stuck</td></tr>
</table>

| | |
|---|---|
| | Disposable detached |
| Maximum infusion pressure | 40 psi |
| Time to Occlusion Alarm | Infusion rate: [redacted] (b) (4)<br>Time to Occlusion Detection: [redacted] |
| Bolus Volume at Occlusion Alarm | Infusion rate: [redacted] (b) (4)<br>Bolus Volume at Occlusion Alarm: [redacted] |
| System Operating Temperature | 2 C to 40 C (35 F to 104 F) |
| System Storage and Transportation Temperature | -20 C to 60 C (-4 F to 140 F) |
| High Pressure Alarm | 26 ± 14 psi |
| [redacted] (b) (4) | |
| Maximum Volume Infused under Single Fault Condition | 0.2mL |

# Safety Engineering Review

**Safety Assurance Case – Introduction**

Given that safety is a system property that cannot be directly measured an argument is required to convince a qualified reviewer that adequate safety has been achieved.

A safety assurance case consists of a structured argument, supported by a body of evidence that provides a compelling, comprehensible and valid case that a medical device is safe for its intended use (e.g. for use on intended patient populations, by intended users, within intended environments of use).

Safety assurance cases (or safety case) are unique to individual products and are dependent on individual product requirements, hazards, design, and documentation and the safety case methodology is fundamentally grounded in safety engineering practice and principles. CDRH began piloting the use of safety cases for infusion pumps in April 2010 in response to increased numbers of infusion pump recalls.

**Review of Adverse Events and Recalls**

I conducted a review of CDRH's adverse event and recall database for issues related to the CADD-Legacy system.

The top reported adverse events are related to leaking of the medication cassette, air bubbles in the cassette, and occluded cassettes.

A corresponding Class II recall (Z-0876-2008) to address the leaking cassettes was opened in 2007 and terminated in 2008.

Issues related to air bubble formation and occlusion will be investigated throughout the review of the device safety case.

**Safety Assurance Case – Review**
Smiths Medical has provided a safety case for the CADD-Legacy 1400 infusion pump.

The primary argument I am interested in to assure an adequately safe design is identified as Argument A110 in the safety case:

*A110: Because all hazards to safety and their associated failure modes and causes have been identified.*

Hazards are categorized by Smiths Medical:

- Under / Over Delivery of Fluid
- Delay of Therapy
- Incorrect Therapy
- Over Pressure
- Infection
- Allergic Response
- Trauma / User Injury
- Excessive Heat or Fire
- Electric Shock or Excessive Patient Leakage Current
- Risks to Environment

This device platform is based on a cleared device and many of the hazards have been addressed in the device system for general use, such as electrical safety, environmental hazards, trauma, sterility, and allergic response. For purposes of this review, I am going to focus on Infusion Delivery Error hazards. This category includes under delivery, over delivery, and delay of therapy hazards.

The hazard analysis assumes 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.

**Infusion Delivery Error.**

**I have conducted a complete review of the hazards analysis documentation (MAF (b) (4) Amendment 3, VOL 6 TAB 10B CADD Legacy 1400 Pump Hazard Analysis) provided for the CADD Legacy 1400 system. I have recorded deficiencies in the analysis in the following table.**

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(b) (4)

[redacted]

**Essential Functional Performance**
Location, CR Response Resubmission letter, page 25-27

It is noted that AbbVie is now labeling the device for programmable infusion rates of 0.4 mL/hr to 20 mL/hr.

**Table 3. System Delivery Accuracy (LCIG)**

| | |
|---|---|
| Therapy[a] | ±10% |
| Continuous Rate[b] | ±10% @ flow rates between 0.4 mL/hr to 20 mL/hr |
| Extra Dose[b] | ±10% |
| Morning Dose[b,c] | ±10% |
| Accessories | 100 mL medication cassette reservoir with 36" 0.10" I.D. tube |

a. Therapy delivery accuracy: program to deliver a 10 mL morning dose with a 5 mL/hr continuous rate and three 3 mL extra doses, with a total of 100 mL of medication delivered. Pumps were evaluated in latch down, upside down, and horizontal position. The medication cassette with Duopa (carbidopa and levodopa enteral suspension) initially is cold (approx. 2°C). Remove cassette from the refrigerator, wait 20 minutes, and then conduct the test at nominal temperature.

b. At nominal temperature (23°C ± 5°C)

c. An additional –4% change may be seen for the morning dose when cassette starting temperature is 2°C and placed at room temperature (23°C ± 5°C) for 20 minutes prior to use.

(b) (4)

[redacted]

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(b) (4)

## IV. Recommended Deficiencies

Complete Review Deficiencies

1. Please 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) respectively. Please clarify the correct accuracy specifications.

**Reviewer Comments: Response is acceptable. The reason for the initial information request was due to inconsistencies in the specifications throughout the submission. The sponsor has clarified**

**the source of the inconsistencies and has clarified the delivery accuracy specifications for the Duopa Pump**

AbbVie Response:
The CADD-Legacy is a family of pumps that includes the CADD-Legacy PCA pump and CADD-Legacy Model 1400 pump. The CADD-Legacy PCA Pump, cleared under premarket notification K982839, has a specified system delivery accuracy and a bolus delivery accuracy of (b) (4) This delivery accuracy specification required adjustment for the Duopa application and the CADD-Legacy Model 1400 Pump. This is because the Duopa drug has a higher viscosity than the medications delivered by the PCA pump.

Therefore, the CADD-Legacy Model 1400 Pump delivery accuracy specification was changed to a therapy delivery accuracy of ±10% and a dose accuracy of (b) (4) The correct accuracy information for the system (continuous rate [continuous maintenance dose], morning dose, and extra dose) were tested and reported under design verification report DVT-1258R-000, the results of which were included in MAF- (b) (4) Amendment 3, TAB 9B (submitted October 30, 2012). Smiths Medical confirms that the dose accuracy specification is ±10%.

Based on the additional testing to address CDRH Issue 1b below, the accuracy specifications have been further refined to reflect clinically relevant test conditions. The results of this testing are documented in DVT-1258R-002 located in MAF- (b) (4) Amendment 5 and Appendix A of this response. The corresponding changes are included in Section 5 of the Operator's Manual (Healthcare Provider Instructions for Use [HCP IFU]), which is located in MAF- (b) (4) Amendment 5 and in Module 1, Section 1.14.1.3, Smiths Pump Ops Manual – Redlined Labeling Text.

**Table 3. System Delivery Accuracy (LCIG)**

| | |
|---|---|
| Therapy[a] | ±10% |
| Continuous Rate[b] | ±10% @ flow rates between 0.4 mL/hr to 20 mL/hr |
| Extra Dose[b] | ±10% |
| Morning Dose[b,c] | ±10% |
| Accessories | 100 mL medication cassette reservoir with 36" 0.10" I.D. tube |

a. Therapy delivery accuracy: program to deliver a 10 mL morning dose with a 5 mL/hr continuous rate and three 3 mL extra doses, with a total of 100 mL of medication delivered. Pumps were evaluated in latch down, upside down, and horizontal position. The medication cassette with Duopa (carbidopa and levodopa enteral suspension) initially is cold (approx. 2°C). Remove cassette from the refrigerator, wait 20 minutes, and then conduct the test at nominal temperature.

b. At nominal temperature (23°C ± 5°C)

c. An additional –4% change may be seen for the morning dose when cassette starting temperature is 2°C and placed at room temperature (23°C ± 5°C) for 20 minutes prior to use.

In addition to the above specifications, the following warning is included in the Operator's Manual (HCP IFU).

WARNING: System delivery inaccuracies beyond the stated accuracy may occur as a result of back pressure or fluid resistance, which depends upon temperature, medication viscosity, catheter size, extension set tubing, flow rates, and orientation of the pump system.

b. The design verification report (DVT-1258R-000) states that the Dose Volume accuracy specification should be updated to [redacted] (b) (4) It is not clear if this recommendation was followed. Please 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, cassette, tubing configuration, drug temperature, etc.

**Reviewer Comments: The response is acceptable. Again, the sponsor has clarified the coorect delivery accuracy specifications and has provided the relevant supporting data.**

AbbVie Response:
The recommendation to update the Dose Volume (Morning Dose and Extra Dose) accuracy specifications to ±10% was followed and the revision of the Operator's Manual (HCP IFU), located in MAF-[redacted] (b) (4) Amendment 4, Appendix 1 reflects this change. AbbVie and Smiths Medical conducted verification testing that supports the administration of Duopa. Supporting data is described below.

Smiths Medical Studies
The studies conducted by Smiths Medical to support the Dose Volume (Morning Dose and Extra Dose) accuracy specifications are listed in Table 4. This testing was performed at room temperature (nominal conditions [23°C historically used for evaluating pumps at Smiths Medical]), which represents the condition the user is going to experience. These studies were provided in MAF-[redacted] (b) (4) Amendment 3 Tab 9B. *(CDRH Reviewer Comment: It is noted that I reviewed this amendment as part of my original review*

*of NDA 203952 and therefore no additional data review is required)* This information was included in the Type A Meeting Information Package submitted on April 11, 2014 to NDA 203952 (Sequence 0031).

**Table 4. Delivery Performance Verification Summary**

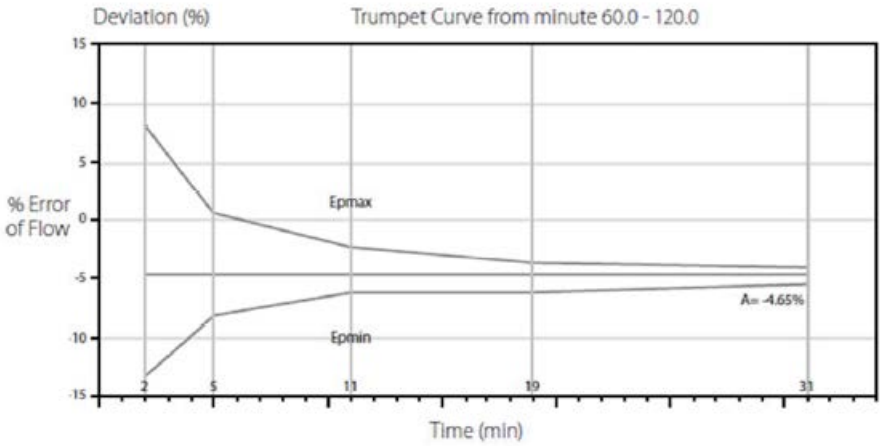
| | Current Specification | Verification Location | Location in MAF-1553 |
|---|---|---|---|
| System Delivery Accuracy | ±10% (nominal) | DVT-1258R-000, Sect. 5.1, Table 1 | Amendment 3, TAB 9B |
| Continuous Rate | ±10% (nominal) | DVT-1258R-000, Sect. 5.1, Figures 1 – 4 | Amendment 3, TAB 9B |
| Extra Dose and Morning Dose | ±10% (nominal) | DVT-1258R-000, Sect. 5.3, Table 4 23°C data | Amendment 3, TAB 9B |

Therapy Delivery Accuracy: The system (therapy) delivery accuracy test results are summarized in DVT-1258R-000, Section 5.1, Table 1. This testing was performed at nominal conditions (23°C), with a morning dose volume of 10 mL, a continuous rate of 5 mL/hr, and 3 extra doses of 3 mL each. The test was run until the 100 mL medication cassette reservoir was empty. Per the test method, LCIG in the 100 mL medication cassette reservoir was pulled from the refrigerator at 2°C and attached to a pump at room temperature (23°C). The pump delivered the LCIG morning dose immediately (with concurrent continuous rate), and then delivered at the continuous rate for 16 hours.

During the 16 hour continuous rate, the three 3 mL extra doses were delivered. The overall system delivery accuracy ranged from (b) (4) % (N = 29), meeting the system specification of ±10% (nominal).

Continuous Rate: Data obtained from performing the continuous delivery accuracy testing at nominal conditions (23°C) are summarized in DVT-1258R-000, Section 5.1, Figures 1 through 4. The same figures were placed into the Operator's Manual in Section 5, under Accuracy Test Results. See Figure 2 below. Data from the trumpet curve shows the flow rate accuracy (mean flow error) at a programmed rate of 5 mL/hr is –4.65%. This testing was performed in accordance with IEC 60601-2-24 (intermediate rate). The results meet the Continuous Rate accuracy specification of ±10% (nominal).

**Figure 2. Trumpet Curve Data in Section 5 of the Operator's Manual (HCP IFU)**




Extra Dose and Morning Dose: Data obtained from performing the dose (i.e., extra dose and morning dose) delivery accuracy testing at volumes of 0.1 mL, 9.9 mL, and 20 mL are summarized in Appendix A, DVT-1258R-002, Section 5.1.3, Table 9. At nominal conditions (23°C), the dose delivery accuracy ranged between (b) (4) %, meeting the extra dose and morning dose accuracy specifications of ±10% (nominal).

As described in response to 1a, the delivery accuracy information has been further refined and is described in Appendix A. The information will also be included in MAF (b) (4) Amendment 5, DVT-1258R Rev. 002 Report.

AbbVie Study
AbbVie has conducted testing that simulates the use of the administration system with LCIG under the anticipated user conditions. A simulated use study (continuous rate over 16 hours) that mimics the daily therapy experience is described in NDA 203952, Module 3, Section 3.2.P.2.6, Compatibility. This testing is summarized in Table 5.

The simulated use studies used representative extension set (tubing) configurations recommended for use with the LCIG system in the NDA 203952, Module 1, Section 1.14.1.3, draft United States Prescribing Information (USPI) and described in NDA 203952, Module 3, Section 3.2.P.2.6, Compatibility, and Section 3.2.P.1,

Description and Composition of Levodopa-Carbidopa Intestinal Gel Administration System.
The environmental conditions for the simulated use testing are described in NDA 203952, Module 3, Section 3.2.P.2.6, Compatibility. In use, the patient will be instructed to remove a drug cassette from refrigerated storage 20 minutes prior to use. This was simulated by removing a cassette from 2°C – 8°C storage and placing it in ambient temperature conditions. The temperature of the tubing that will be inside the patient's body was simulated by submerging that portion of the tubing in a 37°C water bath.

**Table 5. AbbVie Simulated Use Tests**

| Test | Results Location | Results |
|---|---|---|
| Simulated Use – continuous rate over 16 hours (daily therapy) | NDA 203952, Module 3, Section 3.2.P.2.6 | 0.5 mL/hr Accuracy:<br>1 mL/hr Accuracy:<br>10 mL/hr Accuracy:<br>20 mL/hr Accuracy: (b) (4) |

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.

**Reviewer Comments: The sponsor response is adequate to justify the programmable flow rate specifications.**

AbbVie Response:
The pump has a continuous rate operating range of 0.1 to 20 mL/hr (with a ±10% accuracy from 0.4 to 20 mL/hr; refer to response to CDRH Issue 1d for additional details), which is adequate for drug dosing. The dose of LCIG is individually optimized for each patient. Each pump is programmed by the Healthcare Provider (HCP) to deliver the specific amount of drug needed to control the patient's symptoms. (b) (4) However, there is no absolute minimum or maximum dose due to the wide range of severity of symptoms in advanced PD patients. (b) (4) , it is likely that there will be a small percentage of patients who may require lower or higher doses of levodopa to address individual patient needs, as seen in the clinical studies, where the continuous maintenance dose ranged from 0.5 to 12.8 mL/hr. It is therefore appropriate for the pump to be programmable for doses (b) (4) and the range of continuous rates (0.1 to 20 mL) provides maximal flexibility in titrating and managing patients. The increments available for adjusting the continuous dose (0.1 mL/hr) help to facilitate titration during initiation of therapy and to individually optimize dosing for relief of symptoms. These increments of 2 mg/hr of levodopa, are smaller than what can be achieved with oral dosing (with a half-tablet of oral carbidopa-levodopa equating to 50 mg) such that titration to optimal dose can be achieved while minimizing the potential for dyskinesia or other levodopa-related side effects. Based on data from the clinical program, the continuous rate (0.1 – 20 mL/hr) and demand dose (Morning Dose 0 – 20 mL and Extra Dose 0 – 9.9 mL) are also adequate for the purposes of starting therapy in the morning or as rescue to address symptom return during the day (b) (4)

If a patient were to receive a higher dose than what is necessary, this may result in dyskinesia or other known symptoms of levodopa overdose (hallucinations, nausea, vomiting). The development of dyskinesia is a symptom recognized by PD patients who could either stop the pump or reduce the infusion rate with guidance from their HCP or by contacting the Duopa 24-hour helpline for support. Dyskinesia is transient and regularly occurs in most patients with advanced PD on oral treatment. However, there can be a broader array of symptoms for some patients related to increased levodopa

exposure. While mechanisms in the pump prevent risk of serious overdose (such as the pumping of a whole cassette [2 g of levodopa] within a short period of time), these known levodopa-related symptoms would also be transient, and can be managed with limited medical intervention and no long term health outcomes. There are no cases of levodopa overdose in the clinical studies and cases reported from postmarketing are described in Safety Update 2 (R&D/14/0331) Section 10.0, all of which resolved with dose reduction or discontinuation of LCIG. Cases of levodopa overdose, ranging from 1.7 to 50 grams, have been documented in the literature, with no case of death or permanent injury recorded.

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.

**Reviewer Comments: The sponsor has bracketed the flow rates, as requested. They have also modified the programmable minimum specification from (b) (4) mL/hr to 0.4 mL/hr to address the lowest expected clinical infusion rate.**

**The response is acceptable.**

AbbVie Response:
DVT-1258R-000 Section 5.1 was run in accordance with IEC 60601-2-24 (intermediate rate 5 mL/hr) and did not specifically test the minimum and maximum programmable infusion rates. Additional testing has subsequently been completed at the minimum and maximum programmable rates of 0.1 mL/hr and 20 mL/hr. The test results have been added to DVT-1258R-002 (refer to MAF- (b) (4) Amendment 5 and Appendix A of this response). The Operators Manual (HCP IFU) has been updated to align with the new studies (Module 1, Section 1.14.1.3, Smiths Pump Ops Manual – Proposed Labeling Text). The study is summarized below.

Three pumps were tested at 0.1 mL/hr (minimum rate), 0.4 mL/hr, 5 mL/hr, and 20 mL/hr (maximum rate) using production lot cassettes of LCIG. The test was run at nominal temperature conditions (approximately 23°C). Results are summarized below in Table 6. One of the test values at th (b) (4) nimum programmable rate of 0.1 mL/hr exceeds the ±10% criteria with a maximum delivery error of (b) (4) %. This represents a variance of (b) (4) mg of levodopa per hour or (b) (4) mg over 16 hours, neither of which would be expected to be clinically noticeable by the patient (i.e., no physical symptoms of overdose or under dose). However, the lowest continuous rate used in the clinical trial was 0.5 mL/hr, and the rate of 0.1 mL/hr is lower than anticipated clinical use and the recommended lower rate in the USPI. In order to bracket the clinical flow rate used, a test was performed at a flow rate of 0.4 mL/hr rather than 0.5 mL/hr. The results presented in Table 6 show acceptable results at 0.4 mL/hr and therefore, the specification and HCP IFU has been updated to state the pump meets the ±10% at rates of 0.4 mL/hr to 20 mL/hr. The Operators Manual (HCP IFU) has been updated to reflect the results using LCIG (see the response to Issue 1a above and Module 1, Section 1.14.1.3, Smiths Pump Ops Manual – Proposed Labeling Text).

**Table 6. Summary of Continuous Delivery Accuracy (n = 3 per rate)**

| Rate (mL/hr) Over 24 Hours[a] | Average (% Error) | Std Dev (% Error) | Max (% Error) | Min (% Error) |
|---|---|---|---|---|
| 0.1 | | | | (b) (4) |
| 0.4 | | | | |
| 5 | | | | |
| 20 | | | | |

a. This test is specified by IEC 60601-2-24 (1998) clause 50-105: Accuracy test for Infusion Pump for Ambulatory Use Type 2 (non-continuous flow). This procedure indicates to "Allow the Equipment to run for a time equivalent to half the container volume or 24h, whichever is the shorter, as a stabilization period T1 (min)." At the minimum rate of 0.1 mL/hr, 24h is the shorter period for the Legacy 1400 pump system. Additionally, 16h is contained within the 24h testing.

2. We have conducted a review of the software documentation. Please provide the following software documentation for the current release version:

   a. Provide the software revision history document.

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(b) (4)

[redacted]

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 re-tested and that no new anomalies are 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.

**This table addresses all software – related responses.**

**Reviewer Comments: The version history is provided, as requested.**

**The sponsor explanation on unresolved software anomalies and static analyses is thorough and complete. No additional is required at this time, and the response is considered acceptable.**

AbbVie Response:

Regarding Unresolved Anomalies

(b) (4)

[redacted]

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Overall, the results document that Smiths Medical's standard coding practices have been followed and that the software has been soundly designed as per the results of the static analysis.

3. 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 identifies the 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). Column 3 identifies additional information needed to complete our review. Please address the deficiencies identified in column 3.

| **Hazard** - Infusion delivery occurs at an incorrect rate | | |
|---|---|---|
| **Cause** | **Control** | **Deficiency** |

(b) (4)

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(b) (4)

**Reviewer Comments: The response is acceptable.**

**I have updated the safety engineering section of my review to reflect the additional information provided by the applicant.**

AbbVie Response:
In this section, additional information is provided to address the deficiencies raised above in the Hazard Analysis related to the potential for incorrect rate during infusion delivery. In each case, the Hazard Analysis did not need to be changed and is supported appropriately by the additional information, which is available in the referenced requirements and design documents or in the design history file. The Traceability Analyses (MAF (b) (4) Amendment 3, VOL 2 TAB 7) show that each of the controls is verified appropriately.

Review Issues
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 28 psi.

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

AbbVie Response:

a. Originally, time to occlusion was characterized with the CADD-Legacy pump using water. Additional testing has been conducted with the CADD-Legacy Model 1400 pump using LCIG. The results using LCIG are located in MAF (b) (4) Amendment 5: ETR-342. Three pumps were tested at 0.4 mL/hr (representative continuous rate) and 40 mL/hr (Morning/Extra Dose pumping rate) using production lot cassettes of LCIG. The test was run at nominal temperature conditions (approximately 23°C). Results are summarized below in Table 9. The Operators Manual (HCP IFU; Section 5) has been updated to reflect the results using LCIG (Module 1, Section 1.14.1.3, Smiths Pump Ops Manual – Proposed Labeling Text).

**Table 9. Time to Occlusion Alarm**

| Flow Rate | 12 psi | 40 psi | Delta |
|---|---|---|---|
| **Clinical Minimum:** Continuous Rate: 0.4 mL/hr<br>**Clinical Maximum:** Morning and Extra Dose Rate: 40 mL/hr | (b) (4) | | |

b. The occlusion detection alarm specification is set to identify true occlusions. The design has been verified to demonstrate that an occlusion will be detected when the pressure is between 12 – 40 psi (DVT-1258R Rev. 002, MAF (b) (4) Amendment 5 and Appendix A).

In order to evaluate the practical effect of having the high pressure alarm tripped at 12 psi and gain a better understanding of the effect of 28 psi deviation, testing was conducted using LCIG to determine how these pressures relate to time and are summarized in Table 9 above. The results are located in MAF (b) (4) Amendment 5: ETR-342. Based on Table 9 above, therapy could be reduced from the prescribed dose 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 as 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. In this scenario, the patient is instructed to refer to the manual for troubleshooting information or to call the 24-hour helpline for guidance.

4. There appears 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 Gel.

**Reviewer Comments: the response is acceptable**

AbbVie Response:
AbbVie Response:

Earlier information in MAF [redacted] (b) (4) e.g., occlusion alarm time for [redacted] (b) (4) infusion rate, included data related to the CADD-Legacy family of products and is not specific to the CADD-Legacy Model 1400 for use with LCIG.

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 LCIG. Data to support specifications are in Appendix A and in MAF [redacted] (b) (4) Amendment 5 (DVT-1258R Rev. 002 and ETR-342).

5. 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.

**Reviewer Comments: the response is adequate.**

AbbVie Response:

There is no temperature exposure specification during administration of LCIG. The LCIG System is intended for daily use in the home environment and other nonclinical settings by patients. 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 [redacted] (b) (4) Amendment 5 (DVT-1258R Rev. 002).

6. [redacted] (b) (4)

**Reviewer Comments: The response is adequate.**

AbbVie Response:

The specification and safety case are correct as written. (b) (4)

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.

The specifications that are included in Software Specification S97-0365-60, located in MAF (b) (4) Amendment 2, Volume 1, TAB 3, explain that the feature cannot be accessed and also provide a link to the tests that show that it is inactive. (b) (4)

Thus, there is no risk of delayed therapy due to (b) (4) alarms/messages.

## V. Decision Recommendation

All CR deficiencies related to the infusion device have been adequately I addressed. I recommend approval.

| Digital Signature Concurrence Table | | |
|---|---|---|
| Reviewer | Alan M. Stevens -S | Digitally signed by Alan M. Stevens -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S<br>Date: 2014.12.03 16:10:32 -05'00' |
| Team Leader | Ryan J. Mcgowan -S | Digitally signed by Ryan J. Mcgowan -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S<br>Date: 2014.12.03 16:50:03 -05'00' |
| Supervisor | | Digitally signed by Richard C. Chapman -A<br>Date: 2014.12.03 17:07:03 -05'00' |

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

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/s/

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STACY M METZ
12/18/2014

# 505(b)(2) ASSESSMENT

| Application Information | | |
|---|---|---|
| NDA # 203952 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Duopa<br>Established/Proper Name: Levodopa Carbidopa Intestinal Gel (LCIG)<br>Dosage Form: Intestinal Gel<br>Strengths: 20 mg/mL, 5 mg/mL | | |
| Applicant: AbbVie | | |
| Date of Receipt: July 11, 2014 | | |
| PDUFA Goal Date: January 11, 2015 | Action Goal Date (if different):<br>January 9, 2015 | |
| Proposed Indication(s): Long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease [redacted] (b) (4) | | |

## GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

[redacted]



Reference ID: 3675603

## INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
|---|---|
| Sinemet (levodopa-carbidopa) Tablet Label (NDA-17-555) | Clinical studies information.<br>Clinical Pharmacology information.<br>Non-Clinical Toxicology information.<br>Post-marketing data |

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor created a PK model of the population pharmacokinetics of levodopa following administration of LCIG or LC-oral in subjects with advanced Parkinson's disease. The model included PK data combined from the Phase 1 Study S187-1-002 and the Phase 3 pivotal Study S187-3-001/S187-3-002. The model was submitted to establish a bridge between the two carbidopa levodopa formulations (LCIG and oral carbidopa levodopa tablets).

## RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐



Reference ID: 3675603

APPEARS THIS WAY ON ORIGINAL



Reference ID: 3675603

## RELIANCE ON LISTED DRUG(S)

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|---|---|---|
| Sinemet (levodopa-carbidopa) Tablets | NDA 17555 | Yes |
| | | |

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*



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Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Application provides for a new dosage form and new indication.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*



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*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



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Pharmaceutical alternative(s):

## PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*



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☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐



Reference ID: 3675603

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/s/

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STACY M METZ
12/18/2014

**LABELING AND HUMAN FACTORS REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---|---|
| **Date of This Review:** | December 12, 2014 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | NDA 203952 |
| **Product Name and Strength:** | Duopa (Carbidopa and Levodopa Enteral Suspension)<br>Carbidopa 4.63 mg per ml and Levodopa 20 mg per ml |
| **Product Type:** | Combination Product (Drug-Device) |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Abbvie Pharmaceuticals |
| **Submission Date:** | July 11, 2014 |
| **OSE RCM #:** | 2014-1425<br>2014-1748 |
| **DMEPA Primary Reviewer:** | Jacqueline Sheppard, PharmD |
| **DMEPA Acting Team Leader:** | Vicky Borders-Hemphill, PharmD |
| **DMEPA Associate Director:** | Irene Z. Chan, PharmD, BCPS |



Reference ID: 3672267

## 1 REASON FOR REVIEW

Abbvie submitted a Class 2 resubmission on July 11, 2014 to respond to the Complete Response (CR) letter they received on March 28, 2014 for Duopa. The CR letter, in part, required additional changes to the product-user interface[1] as well as another human factors summative study to validate these changes. Thus, this resubmission includes the results of a Human Factors usability validation study of Duopa (Carbidopa and Levodopa Enteral Suspension), which the Division of Neurology Products (DNP) asked us to review. This review also responds to the additional request from DNP to evaluate the Prescribing Information, Medication Guide, (b) (4) container label and carton labeling for the Duopa (Carbidopa and Levodopa Enteral Suspension) submitted on October 31, 2014, for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

**Table 1. Materials Considered for this Label and Labeling Review**

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| FDA Adverse Event Reporting System (FAERS) | B – N/A |
| Previous DMEPA Reviews | C |
| Human Factors Study | D |
| ISMP Newsletters | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Abbvie Pharmaceuticals made revisions to the Instructions for Use (IFU) and tested the revisions in a summative human factors (HF) study. The revisions were made to address specific failures that occurred in the summative study submitted on May 28, 2013 and human

[1] See Appendix D for changes made to Instructions for Use



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factor deficiencies outlined in the CR letter. Deficiencies addressed included health care provider understanding and programming of lock levels, patient understanding of warning and caution statements, and health care provider understanding and performance with general programming and programming related to patient dose adjustment (see Appendix D- Table 4).

The summative Human Factors (HF) study results were submitted on July 11, 2014. All participants (9 healthcare providers (HCP) and 6 patients) in the study successfully completed critical tasks associated with pump connections, extra dose, evening procedure, changing the cassette, alarms and messages, warning and caution statements, and programming pump system and setting lock levels for patient use (HCP only tasks). There was a failure in the critical task of patient adjustment of the morning dose. This same failure was previously seen in the summative study submitted in 2013. Although this particular error is still occurring, we believe the improvements made to the IFU and the addition of a toll free helpline has further reduced the risk, and the risk has been mitigated to an acceptable level for this product. The study results are limited by the small number of participants (n=15 inclusive of all user groups) in each distinct user group. Thus, we looked holistically at the overall performance of the Duopa System by also considering the study results submitted May 28, 2013 for those tasks that were not affected by changes to the product-user interface. Overall, the study results suggest that Duopa Enteral Suspension can be used safely and effectively by healthcare professionals and by patients with advanced Parkinson's disease.

In an information request sent October 9, 2014, DMEPA asked the Applicant to clarify whether there are instructions available for patients who need to disconnect the pump for brief disruptions due to medical procedures or activities of daily living (e.g., MRI, showering and bathing, etc). In the response dated October 15, 2014, the Applicant submitted language to address disruption of therapy for shorter periods of time due to medical procedures or activities of daily living. We recommend revising the language for clarity and improved readability and adding it to Section 2.3 of the Prescribing Information (Interruption of Infusion) and the Medication Guide. We will not require these changes be validated in an additional human factors study; however, we will monitor post-market for any errors related to disruption of therapy. In the summative human factors study, patients demonstrated the ability to disconnect the system. This new information will add to user knowledge as to when to disconnect the system.

(b) (4)



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(b) (4)

Assessment of Labels and Labeling

We identified areas of the insert labeling, carton labeling and container labels that can be revised to increase clarity, improve readability, add important critical information, or increase prominence of important information.

(b) (4)

The strength of the product is expressed per milliliter, and the pump is also programmed based on milliliters. (b) (4) We recommend the net quantity statement is changed to reflect milliliters for consistency.

We note that the proposed strength for this product is "4.63 mg/mL and 20 mg/mL." Although we did not identify another enteral solution for comparison, other currently marketed oral solutions comprised of more than one active ingredient present the strength as a single statement separated by slashes. For example, Bactrim's strength is presented as 200mg/40mg/5ml and Tylenol with Codeine's strength is presented as 120mg/12mg per 5 ml. This suggests that the strength for Duopa could be presented as 4.63 mg/20 mg per mL or 4.63 mg/20 mg/mL. We recommend DNP consults the Chemistry and Manufacturing Controls Reviewer concerning the presentation of strength.

## 4 CONCLUSION & 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 submitted labels and labeling for Duopa can be revised to communicate important use information, increase the prominence of important product information, and improve readability and clarity. We recommend the following revisions are implemented prior to the approval of this NDA.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

**A. Prescribing Information and Medication Guide**

1. Section 2 (Dosage and Administration) and Medication Guide

    a. We recommend that instructions for temporary discontinuation of Duopa are included in section 2.3 (Interruption of Infusion) of the Prescribing Information



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and in the Medication guide. Additionally, we recommend this subsection is further subdivided into "extended periods of disconnection time" (e.g., pump breakage, no shipment of medicine, etc.) and "short term disconnections" (e.g., MRI, showering). The PI provides some instructions for temporary discontinuation of medication; however, the instructions do not give clear timelines on what constitutes a temporary discontinuation (e.g., 30 minute bath versus 2 hour MRI or 3 days for a broken pump). We recommend this is clarified in the labeling.

2. Section 16 (How Supplied/Storage and Handling) and Medication Guide

   a. In Section 16.2 (Storage), we recommend increasing the prominence of the directions for determining the 12 week discard date. This product must be used within 12 weeks after being thawed and stored in the refrigerator or the product will degrade. This information is currently easily overlooked and the unintentional omission may lead patients to use deteriorated drug product.

   b. In Section 16.2 (Storage), we recommend using subheadings to divide the section into a section for dispensing pharmacies and a section for pharmacists and nurses in a hospital or nursing care setting. The product will be shipped frozen to the pharmacist, and then thawed in the refrigerator before dispensing to the patient. The dispensing pharmacy section should contain storage, thawing, and use-by dating instructions. The hospital or nursing care setting should contain refrigeration and instructions for use at room temperature.

   c. We recommend a reminder that the product be used at room temperature should be placed in the Medication guide (How Should I store Duopa). Omission of this step and failure to use the product at room temperature may clog the pump and lead to pump failure.

   d. We recommend DNP consults the Chemistry and Manufacturing Controls Reviewer concerning the presentation of strength. Although we did not identify another enteral solution for comparison, other currently marketed oral solutions comprised of more than one active ingredient present the strength as a single statement separated by slashes. This suggests that the strength for Duopa could be presented as 4.63 mg/20 mg per mL or 4.63 mg/20 mg/mL.



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## 4.2 RECOMMENDATIONS FOR THE APPLICANT

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 (b) (4) as the dosing calculation provided in Section 2 are provided in volume (e.g., 100 ml (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 (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.

(b) (4)



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## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Duopa that Abbvie Pharmaceuticals submitted on July 11, 2014.

| **Table 2. Relevant Product Information for Duopa** [redacted] (b) (4) | |
|---|---|
| **Active Ingredient** | Carbidopa and Levodopa |
| **Indication** | Long-term treatment of motor fluctuations in patients with advanced Parkinson's disease |
| **Route of Administration** | Intrajejunal |
| **Dosage Form** | Enteral suspension |
| **Strength** | 4.63 mg/ml carbidopa monohydrate and 20 mg/ml levodopa |
| **Dose and Frequency** | ! Duopa is administered as a bolus in the morning, followed by a continuous infusion for up to 16 hours. Additional bolus doses are administered throughout the day as needed by the patient.<br>○ The morning dose [redacted] (b) (4)<br>○ The continuous maintenance dose [redacted] (b) (4)<br>○ Extra doses are [redacted] (b) (4)<br>○ [redacted] (b) (4) |
| **How Supplied** | ! Each mL contains 20 mg levodopa and 5 mg carbidopa monohydrate. The gel is supplied in cassettes of approximately 100 grams. Carton of 7 medication cassettes. |
| **Storage** | ○ Duopa is stable for 24 months at –20°C (–4°F) and [redacted] (b) (4) weeks at 5°C (41°F).<br>○ The product is shipped frozen to the dispensing pharmacy and will be sent to the patient thawed at 5°C. |



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| | |
|---|---|
| | o Duopa should be thawed and stored in the refrigerator at 36°F to 46°F (2°C to 8°C). Under these conditions, Duopa remains stable for up to (b) (4) weeks. |

## APPENDIX C. PREVIOUS DMEPA REVIEWS

### C.1 Methods

We searched the L: Drive on October 28, 2014 using the term, Duopa, to identify reviews previously performed by DMEPA.

### C.2 Results

We identified five previous reviews concerning Duopa that were conducted by DMEPA:

1. Sheppard, J. Type A Pre-NDA Meeting for Duopa (Carbidopa and Levodopa Enteral Suspension) (NDA 203952). FDA/CDER/OSE/DMEPA. 2014 June 3. 3 p. RCM 2014-812
2. Cantin, J. Proprietary Name Review of Duopa (Carbidopa and Levodopa Intestinal Gel) (IND 60663). FDA/CDER/OSE/DMEPA. 2010 May 17. 38 p. RCM 2009-2426.
3. Liu, L. Proprietary Name Review of Duopa (Carbidopa and Levodopa Intestinal Gel) (NDA 203952). FDA/CDER/OSE/DMEPA. 2013 Sept 4. 43 p. RCM 2013-1402.
4. Neshiewat, J. Usability Study, Label, and Labeling Review of Duopa (Carbidopa and Levodopa Enteral Suspension) (NDA 203952). FDA/CDER/OSE/DMEPA. 2014 Feb 21. 23 p. RCM 2013-1403.
5. Sheppard, J. Proprietary Name Review of Duopa (Carbidopa and Levodopa Enteral Suspension) (NDA 203952). FDA/CDER/OSE/DMEPA. 2014 Oct 27. 20 p. RCM 2014-26201.

## APPENDIX D. HUMAN FACTORS STUDY

**Part A: Summative Study submitted July 11, 2014**

### D.1 Objective

The primary objective of the study was to validate if Duopa is safe and effective for use by the intended user population without unspecified patterns or preventable use errors or difficulties that could result to harm to the end user.



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The secondary objective of this study was to validate that recent modifications to the IFU and training methods informed by the previous study were evaluated for their effectiveness to mitigate use errors without presenting new risks.

### D.2 Study Population

15 total participants consisting of:

- 6 Naïve Duopa patients who attended 3 training sessions and 1 testing session
- 9 HCP (specialty pharmacists, RN, NP) who attended 2 training sessions and 1 testing session

### D.3 Design

Participants did receive formal training on the device consistent with the model for clinical practice. The study included one on one sessions consisting of training and testing. In the training sessions, advanced Parkinson's Disease (PD) patients were given the Duopa system, IFU and guidance from certified nurse educators. The time and training was representative of planned commercial training. In the testing sessions, participants were given the Duopa system and asked to perform critical tasks using IFUs and support materials without guidance from moderator.



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## D.4 Human Factors and Usability Results

*Table 3. Duopa Human Factor Results on Critical Tasks*

| Duopa Human Factors Results on Critical Tasks (Total Events Associated with Critical Tasks) | | | | |
|---|---|---|---|---|
| | Supplemental HF Study | | | |
| | Patients (N = 6) | | HCP (N = 9) | |
| Use Scenario | Task Failures | Close Calls | Task Failures | Close Calls |
| Morning Procedure | 0 | 0 | 0 | 0 |
| Extra Dose | 0 | 0 | 0 | 0 |
| Evening Procedure | 0 | 0 | 0 | 0 |
| Change Cassette | 0 | 0 | 0 | 0 |
| Adjust Morning Dose | 1 | 0 | 0 | 0 |
| Adjust Continuous Rate | 0 | 0 | 0 | 0 |
| Alarms and Messages | 0 | 0 | 0 | 0 |
| Warnings and Caution | 0 | 0 | 0 | 0 |
| Pump Programming | Not applicable | | 0 | 0 |
| Set Lock Level for Patients | Not applicable | | 0 | 0 |
| Change Batteries | Evaluated in the original HF study | | | |

All participants completed all tasks associated with the extra dose, evening procedure, changing the cassette, alarms, and programming system for patient use (HCP only task). The identified errors related to Duopa Enteral Suspension System are detailed below.

Failure to Adjust Morning Dose (n=1)

One patient failed to adjust the Morning dose correctly due to slowness of progressing between steps. The participant successfully completed the scenario later during testing.



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Detailed Summary of Failure

P2 was unsuccessful on his first attempt to adjust the Morning Dose as he delivered the previously programmed Morning Dose rather than a newly adjusted dose. P2 followed the Patient IFU and performed the steps correctly to adjust the morning dose but he did not press the Enter/Clear button within 25 seconds to confirm the dose adjustment. After 25 seconds, the pump reverted back to the original Morning Dose. P2 pressed the Enter/Clear button after 28 seconds. P2 recognized that the original Morning Dose was displayed after he pressed the Enter/Clear button and not the Morning Dose he intended. P2 attempted to repeat the Patient IFU steps; however, he went back too far in the Patient IFU and pressed the Morning Dose button again. This resulted in delivery of the original Morning Dose, not the intended adjusted dose. P2 recognized something was not right and stated he would call the helpline for assistance. P2 correctly told the helpline operator the task he was performing and where he was in the Patient IFU. He did not realize the Morning Dose was being administered. He told the helpline nothing happened when he pressed Morning Dose. P2 was told that the Morning Dose had been administered and was now locked out. At this time, P2 reported that he would call an HCP and ask what to do.

After the other study scenarios and questions were completed, the Adjust Morning Dose scenario was repeated and P2 completed it successfully.

## D.4 Instruction for Use Changes

Revisions to the IFU based on the Complete Response Letter

The specific changes made to the IFU for the Duopa system are detailed below.



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*Table 4. Revisions to the IFU based on the CRL*

| Usability Issue | Mitigation Implemented and Tested in Supplemental Study |
|---|---|
| HCP Morning Dose programming error | HCP IFU, pages 23 and 74, revised for improved clarity on this step and additional Caution to HCP message added. |
| Failure to administer the Morning Dose | Patient IFU, page 7, and HCP IFU, page 33, revised for organization and clarity that there are two separate button presses needed to complete this step. |
| Failures with Changing the Cassette | Patient IFU, pages 14 to 18, text revised to improve organization of task flow of directions on how to change the cassette. |
| Failures to flush the PEG-J tubing | Patient IFU, page 12, text revised to improve organization of task flow of directions on how to flush the tube. |
| HCP confusion regarding lock level table in HCP IFU | HCP IFU, pages 9 and 10, revised into two separate tables for improved clarity on what functions are available in which lock level. |
| Recommendations to Patient IFU:<br>• Include a statement to administer enteral nutrition through a different port.<br>• Use one consistent term for the Duopa cassette.<br>• Revise terms, such as [redacted] (b) (4) for more patient friendly language.<br>• Clarify and justify statement that failure to properly follow warnings, cautions, and instructions could result in death. | Revisions Made to the Patient IFU:<br>• Page 1: Statement to administer enteral nutrition through a different port.<br>• Page 2 and throughout: Consistently used term Duopa cassette.<br>• Page 3 and throughout: Revised terms for more patient friendly language; Term [redacted] (b) (4) removed.<br>• Page 3: Statement that failure to properly follow warnings, cautions, and instructions could result in death clarified to state in extreme cases |
| • Add statement that the proposed pump should only be used with approved carbidopa and levodopa enteral suspension cassettes.<br>• Remove [redacted] (b) (4) as examples of pump screen shots. | • Pages 3, 4, 14: Statement added that the proposed pump should only be used with approved Duopa cassettes.<br>• Pages 7, 23, 24: Removed [redacted] (b) (4) as examples of pump screen shots. |
| Recommendations to the HCP IFU:<br>• Combine two instructional materials for HCPs into one document. | Revisions to the HCP IFU:<br>• Page 71 to 75: Added appendix to Smiths Operators Manual to combine [redacted] (b) (4) into single IFU for HCPs. |

Appears this way on original

| Usability Issue | Mitigation Implemented and Tested in Supplemental Study |
|---|---|
| Product Design Recommendations: | Revisions Made to Patient IFU and/or HCP IFU: |
| • Develop an alarm feature to alert patients when cassette is empty. | • To be considered in future development |
| • Consider designing the pump so the morning dose button only has to be depressed once for delivery. | • Patient IFU, page 7, and HCP IFU, page 33 revised for organization and clarity that there are two separate button presses needed to complete this step. |
| • Consider revising the pump software so the morning dose can be programmed in stop mode. | • HCP IFU, pages 23 and 74, revised to improve clarity that programming the morning dose needs to be done while the pump is running. |
| • Deactivate certain features in the pump software that patients or HCPs do not use, such as the Reservoir Volume function. | • HCP IFU, pages 6, 20, 22, 35 and 72, added note that reservoir volume feature is optional and default setting is 'Not In Use.' |

Specific concerns that were addressed include replacing the single lock level table with two tables to improve readability and clarify which functions can be performed with each lock level. Additional changes included combining and simplifying warning and precautions in the patients' IFU by utilizing simple language and providing screen shots for HCP programming tasks and patient dose adjustment tasks.

**Part B: Summative Studies Performed by Applicant**

The following chart is a compilation of summative Human Factor usability studies associated with this application.

*Table 5. Human Factors (HF) Studies*

| HF Study Name | NDA Location | Referred to Within this Resubmission as: |
|---|---|---|
| HF Engineering/Usability Engineering Summary Report for Levodopa/Carbidopa Intestinal Gel Administration System Essential Tasks (Included the Primary Validation and Lock Level I Supplemental Studies) | NDA 203952, Module 3, Section 3.2.R (Seq. 0015, May 2013) | Original HF Study |
| Lock Level 1 Supplemental Study | Included within Original HF Study | Lock Level Study |
| Duopa Supplemental Human Factors Validation Study Report | NDA 203952, Module 3, Section 3.2.R (Seq. 0033, July 2014) | Supplemental HF Study |
| Integrated Human Factors Validation Summary Report | NDA 203952, Module 3, Section 3.2.R (Seq. 0033, July 2014) | Integrated HF Summary (this report) |



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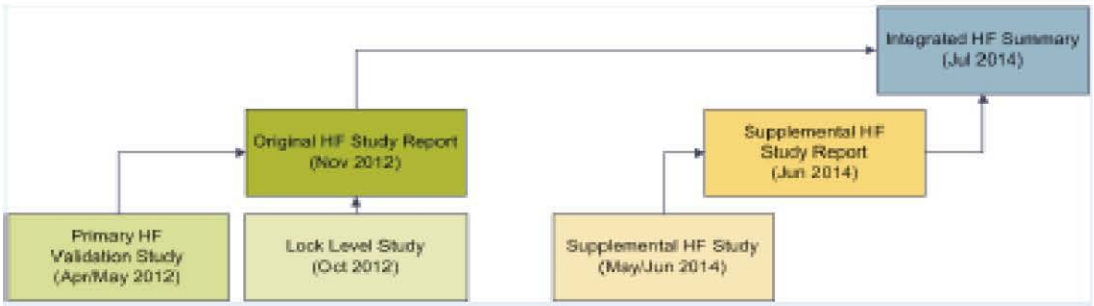
Figure 1. Human Factors (HF) Studies






Reference ID: 3672267

*Table 6. Duopa HF Total Events Associated with Critical Task Events*

| | Original HF Study | | | | Supplemental HF Study | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients (N = 25) | | HCP (N = 25) | | Patient (N = 6) | | HCP (N = 9) | |
| Use Scenario | Task Failures | Close Calls | Task Failures | Close Calls | Task Failures | Close Calls | Task Failures | Close Calls |
| Morning Procedure | 2 | 3 | 3 | 2 | 0 | 0 | 0 | 0 |
| Extra Dose | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Evening Procedure | 2[a] | 3 | 3 | 0 | 0 | 0 | 0 | 0 |
| Change Cassette | 4[a] | 1 | 2 | 1 | 0 | 0 | 0 | 0 |
| Adjust Morning Dose | 6[a] | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Adjust Continuous Rate | 1[a] | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Alarms and Messages | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Warnings and Caution | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pump Programming | Not applicable | | 3 | 9[a] | Not applicable | | 0 | 0 |
| Set Lock Level for Patients | Not applicable | | 0 | 1 | Not applicable | | 0 | 0 |
| Change Batteries | 1 | 0 | 0 | 0 | Not Assessed | | | |
| Total Critical Task Failures/Close Calls | 17[a] | 7 | 11 | 13[a] | 1 | 0 | 0 | 0 |

a. Value includes test artifacts. Test artifacts are events not related to actual use of the system but by-products of simulated-use testing. Of the 29 total task failures, 9 were test artifacts and of the 20 total close calls, 7 were test artifacts.

- 1 task failure, Evening Procedure
- 1 task failure, Change the Cassette
- 6 task failures, Adjust Morning Dose
- 1 task failure, Adjust Continuous Rate
- 7 close calls, Pump Programming



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**Overall Conclusions:**

1. All participants successfully completed tasks associated with morning procedure, extra dose, evening procedure, changing cassette, alarms, programming system for patient use (HCP only task)
2. One patient failed to adjust the Morning dose correctly due to slowness of progressing between steps. He successfully completed the scenario later during testing.



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## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Duopa (Carbidopa and Levodopa Enteral Suspension) labels and labeling submitted by Abbvie Pharmaceuticals on July 11, 2014 and October 31, 2014.

Carton Labeling

(b) (4)

[redacted]

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



Reference ID: 3672267

Cassette Label

(b) (4)

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/s/

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JACQUELINE E SHEPPARD
12/12/2014

BRENDA V BORDERS-HEMPHILL
12/12/2014

IRENE Z CHAN
12/12/2014

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | December 10, 2014 |
| To: | Billy Dunn, M.D.<br>Acting Director<br>**Division of Neurology Products (DNP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Shawna Hutchins, MPH, BSN, RN<br>Acting Team Leader, Patient Labeling Team<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Robin Duer, MBA, BSN, RN<br>Acting Team Leader, Patient Labeling Team<br>**Division of Medical Policy Programs (DMPP)**<br><br>Twanda Scales, RN, MSN/Ed.<br>Patient Labeling Reviewer, Patient Labeling Team<br>**Division of Medical Policy Programs (DMPP)**<br><br>Melinda McLawhorn, PharmD, BCPS<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU) |
| Drug Name (established name): | DUOPA (carbidopa and levodopa) |
| Dosage Form and Route: | enteral suspension for intrajejunal use |
| Application Type/Number: | 203952 |
| Applicant: | Abbvie Inc. |

# 1 INTRODUCTION

On July 11, 2014, Abbvie Inc. submitted for the Agency's review a Complete Response for New Drug Application (NDA) 203952 for DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use, indicated for the long-term treatment of motor fluctuations in patients with advanced idiopathic Parkinson's disease.

NDA 203952 was originally submitted to the Agency on May 28, 2013. Reference is made to the Agency's Complete Response Letter for this NDA dated March 28, 2014. Abbvie's July 14, 2014 submission is in response to all issues and deficiencies identified by the Agency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on July 30, 2014, and July 29, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

# 2 MATERIAL REVIEWED

- Draft DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use MG and IFU received on July 11, 2014 and received by DMPP on November 24, 2014.
- Draft DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use Prescribing Information (PI) received on July 11, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on November 24, 2014.
- Draft DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use MG and IFU received on July 11, 2014 and received by OPDP on November 24, 2014.
- Draft DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use Prescribing Information (PI) received on July 11, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on November 24, 2014.
- DMEPA review of the DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use Human Factors Study protocol dated February 21, 2014

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- DMPP recommends that CDRH be consulted to review this device. DMPP does not review or comment on devices or pumps or mechanical instructions specific to devices or pumps and its functioning, or other information unrelated to a drug.
- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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TWANDA D SCALES
12/10/2014

MELINDA W MCLAWHORN
12/10/2014

ROBIN E DUER
12/10/2014

SHAWNA L HUTCHINS
12/10/2014

LASHAWN M GRIFFITHS
12/10/2014

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

## Memorandum

**Date:** December 8, 2014

**To:** Tracy Peters, PharmD
Regulatory Project Manager
Division of Neurology Products (DNP)
Office of Drug Evaluation (ODE)-I

**From:** Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Mathilda Fienkeng, PharmD
Team Leader, OPDP

**Subject:** **NDA 203952**
**DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use**

---

**Background**

On July 29, 2014, DNP consulted OPDP to review the draft package insert (PI), medication guide (MG), patient and healthcare provider instructions for use (IFU), and carton and container labeling for the original NDA submission for DUOPA (carbidopa and levodopa enteral suspension), for intrajejunal use.

OPDP reviewed the draft substantially complete version of the PI and healthcare provider IFU provided by DNP on November 24, 2014 and the carton and container labeling retrieved from the electronic document room. Our comments on the PI, healthcare provider IFU, and carton and container labeling are provided below. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the MG and patient IFU under a separate cover.

Thank you for your consult. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.



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Reference ID: 3669598

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MELINDA W MCLAWHORN
12/08/2014

**DEPARTMENT OF HEALTH AND HUMAN SERVICES** **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

# CDRH Human Factors Review

*** This document contains proprietary information that cannot be released to the public***

DATE: October 17, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Gerald Podskalny, Medical Officer, CDER/OND/ODEI/DNP
Tracy Peters, Regulator Project Manager, CDER/OND/ODEI/DNP

SUBJECT: **NDA 203952**
Applicant: AbbVie Inc.
Device Constituent: Infusion Pump
Drug Constituent: Levodopa/Carbidopa Intestinal Gel
Intended Treatment: Parkinson's disease
CDRH CTS Tracking No.: ICC 1300476

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Date: 2014.10.17 15:05:32 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.10.17 15:14:56 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

# CDRH Human Factors Review

### *Overview and Recommendation*

The Division of Neurology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of a supplementatl human factors validation study report submitted under the NDA resubmission, #203952, by AbbVie. The device constituent is an infusion pump (CADD-Legacy Model 1400 pump) and it is used to administer Levodopa-carbidopa intestinal gel, which is indicated for long term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)

On 3/28/2014, FDA issued a Complete Response Letter (CRL) to AbbVie stating deficiencies associated with product quality, device/engineering, and human factors validation study report that required modification and revalidation. AbbVie was requested to resolve the design and engineering deficiencies concerning the pump before initiating a supplemental human factors study. AbbVie subsequently submitted a draft protocol for the supplemental human factors study for Agency's review and feedback. Please see Attachment 2 for prior CDRH HF reviews on the study protocol and on the original HF study report.

On 7/11/2014, AbbVie submitted the NDA resubmission providing a complete response to the deficiencies. Please see evaluation of Abbvie's response to deficiencies in Attachment 1. To address the human factors deficiencies, AbbVie modified the patient and healthcare provider Instructions for Use and training program, and revalidate these modifications in a supplemental human factors validation study. In addition, AbbVie also submitted an integrated human factors report that summarizes all of human factors validation activities performed on the proposed product to-date.

This supplemental simulated-use validation test was conducted with 15 participants – 9 Duopa naïve HCPs and 6 Duopa naïve patients. All participants received training and returned 1 day after to perform the testing. The supplemental human factors (HF) study was conducted as a complementary study to validate product modifications implemented after the original HF study. The supplemental HF study results showed one failure in the patient group. This participant was unsuccessful on his first attempt to adjust the Morning Dose as he delivered the previously programmed Morning Dose rather than a newly adjusted dose. The participant recognized something was not right and stated he would call the helpline for assistance. After the other study scenarios and questions were completed, the Adjust Morning Dose scenario was repeated and this participant completed it successfully.

**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.**



Reference ID: 3648488

# CDRH Human Factors Review

## Combination Product Device Information

**Submission No.:NDA 203952**
Applicant: AbbVie Inc.
Device Constituent: Infusion Pump
Drug Constituent: Levodopa/Carbidopa Intestinal Gel
Intended Treatment: Parkinson's disease

## CDRH Human Factors Involvement History

- 6/4/2013 – CDRH HFPMET was requested to review the human factors validation study report included in the NDA. Review Materials:
  EDR Location: \\CDSESUB1\EVSPROD\NDA203952\203952.enx
- 12/23/2013 – CDRH HFPMET provided information requests to obtain clarification and additional information. AbbVie provided additional information on 1/29/2014 and 2/10/2014.
- 3/28/2014 – FDA issued a Complete Response Letter outlining multiple human factors, device/engineering, and product quality issues.
- 4/23/2014 – CDRH HFPMET was requested to review the draft human factors validation study protocol. This protocol was submitted as part of type A meeting request to ensure alignment with FDA to address Complete Response decision issued during the last review cycle.
- 5/9/2014 – CDRH HFPMET provided CDER a list of deficiencies to be communicated to the Sponsor.
- 7/25/2014 – CDRH HFPMET was requested to review the human factors information contained in the NDA resubmission available at \\CDSESUB1\evsprod\NDA203952\0033
- 10/17/2014 - CDRH HFPMET provided review recommendation to CDER/DNP.

## Summary of Human Factors Related Information

This supplemental simulated-use validation test was conducted with 15 participants – 9 Duopa naïve HCPs and 6 Duopa naïve patients. All participants received training and returned 1 day after to perform the testing. The supplemental human factors (HF) study was conducted as a complementary study to validate product modifications implemented after the original HF study. The modifications included:

- 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 HCP-Duopa trainer interactions in clinical practice
- Educational and support materials, including
  - Educational materials based on the IFU
  - Duopa patient videos
  - Helpline available to patients and HCPs

AbbVie reported that a comprehensive patient and physician support program that will be available upon approval to provide training and services for the use of Duopa. Patient and physician 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



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initiation. This training requires that patients independently demonstrate understanding of tubing care, pump operation and daily routines, and on-going care of Duopa. Additionally, a 24-hour helpline will be available to respond to patient or HCP questions on daily use of the Duopa system, pump alarms, and product maintenance. HCPs will also receive in-depth, interactive training consistent with the HCP IFU and other product labeling to provide supplemental education on the use of Duopa. Please see table 1 below showing the additional mitigations that were implemented prior to the supplemental HF study.

| **Usability Issue** | **Mitigation Implemented and Tested in Supplemental Study** |
|---|---|
| HCP Morning Dose programming error | HCP IFU, pages 23 and 74, revised for improved clarity on this step and additional Caution to HCP message added. |
| Failure to administer the Morning Dose | Patient IFU, page 7, and HCP IFU, page 33, revised for organization and clarity that there are two separate button presses needed to complete this step. |
| Failures with Changing the Cassette | Patient IFU, pages 14 to 18, text revised to improve organization of task flow of directions on how to change the cassette. |
| Failures to flush the PEG-J tubing | Patient IFU, page 12, text revised to improve organization of task flow of directions on how to flush the tube. |
| HCP confusion regarding lock level table in HCP IFU | HCP IFU, pages 9 and 10, revised into two separate tables for improved clarity on what functions are available in which lock level. |
| Recommendations to Patient IFU:<br>• Include a statement to administer enteral nutrition through a different port.<br>• Use one consistent term for the Duopa cassette.<br>• Revise terms, such as [redacted] (b) (4) for more patient friendly language.<br>• Clarify and justify statement that failure to properly follow warnings, cautions, and instructions could result in death.<br>• Add statement that the proposed pump should only be used with approved carbidopa and levodopa enteral suspension cassettes.<br>• Remove [redacted] (b) (4) as examples of pump screen shots. | Revisions Made to the Patient IFU:<br>• Page 1: Statement to administer enteral nutrition through a different port.<br>• Page 2 and throughout: Consistently used term Duopa cassette.<br>• Page 3 and throughout: Revised terms for more patient friendly language; Term [redacted] (b) (4) removed.<br>• Page 3: Statement that failure to properly follow warnings, cautions, and instructions could result in death clarified to state in extreme cases.<br>• Pages 3, 4, 14: Statement added that the proposed pump should only be used with approved Duopa cassettes.<br>• Pages 7, 23, 24: Removed [redacted] (b) (4) as examples of pump screen shots. |
| Recommendations to the HCP IFU:<br>• Combine two instructional materials for HCPs into one document. | Revisions to the HCP IFU:<br>• Page 71 to 75: Added appendix to Smiths Operators Manual to combine [redacted] (b) (4) [redacted] (b) (4) into single IFU for HCPs. |
| Product Design Recommendations:<br>• Develop an alarm feature to alert patients when cassette is empty.<br>• Consider designing the pump so the morning dose button only has to be depressed once for delivery.<br>• Consider revising the pump software so the morning dose can be programmed in stop mode.<br>• Deactivate certain features in the pump software that patients or HCPs do not use, such as the Reservoir Volume function. | Revisions Made to Patient IFU and/or HCP IFU:<br>• To be considered in future development<br>• Patient IFU, page 7, and HCP IFU, page 33 revised for organization and clarity that there are two separate button presses needed to complete this step.<br>• HCP IFU, pages 23 and 74, revised to improve clarity that programming the morning dose needs to be done while the pump is running.<br>• HCP IFU, pages 8, 20, 22, 35 and 72, added note that reservoir volume feature is optional and default setting is 'Not In Use.' |

Table 1: Additional Mitigations/Changes to Product User Interface



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The following table shows the supplemental HF study results:

| Duopa Human Factors Results on Critical Tasks (Total Events Associated with Critical Tasks) | | | | |
|---|---|---|---|---|
| | Supplemental HF Study | | | |
| | Patients (N = 6) | | HCP (N = 9) | |
| Use Scenario | Task Failures | Close Calls | Task Failures | Close Calls |
| Morning Procedure | 0 | 0 | 0 | 0 |
| Extra Dose | 0 | 0 | 0 | 0 |
| Evening Procedure | 0 | 0 | 0 | 0 |
| Change Cassette | 0 | 0 | 0 | 0 |
| Adjust Morning Dose | 1 | 0 | 0 | 0 |
| Adjust Continuous Rate | 0 | 0 | 0 | 0 |
| Alarms and Messages | 0 | 0 | 0 | 0 |
| Warnings and Caution | 0 | 0 | 0 | 0 |
| Pump Programming | Not applicable | | 0 | 0 |
| Set Lock Level for Patients | Not applicable | | 0 | 0 |
| Change Batteries | Evaluated in the original HF study | | | |

Table 2: Supplemental HF Study Results

There was one failure observed in the study in the patient group. This participant was unsuccessful on his first attempt to adjust the Morning Dose as he delivered the previously programmed Morning Dose rather than a newly adjusted dose. He did not press the Enter/Clear button within 25 seconds to confirm the dose adjustment. After 25 seconds, the pump reverted back to the original Morning Dose. This resulted in delivery of the original Morning Dose, not the intended adjusted dose. The participant recognized something was not right and stated he would call the helpline for assistance. After the other study scenarios and questions were completed, the Adjust Morning Dose scenario was repeated and this participant completed it successfully.



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## Attachment 1: CDRH Human Factors Review of Abbvie's Response to CRL

This appendix includes the HF deficiencies in the CRL, a summary of Abbvie's response, and this reviewer's evaluation of the response.

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. 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.
**Summary of Response: AbbVie implemented revised IFUs for the patient and health care provider (HCP), and training that more closely mimicked the training in clinical practice and evaluated them in a supplemental HF study. The supplemental study showed reduced use error and improved overall user performance on critical tasks. <u>This response was found acceptable.</u>**

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.
**Summary of Response: Response and interpretation to the alarms/messages (shown in the table below) listed in the IFUs, including the high pressure and low battery alarms/messages are not unique in what is required from the user (HCP and patient) to address the alarm. The high pressure alarm represents a repeating two-tone alarm with immediate action required and the low battery alarm represents a single two-tone alarm with no immediate action required. These 2 alarms/messages are representative of all other alarms/messages the patient could experience in tone or action.**

| Repeating Two Tone Alarm/Message with Immediate Action Required | Two Tone Alarms with No Immediate Action Required |
|---|---|
| High Pressure | Low Battery |
| Upstream Occlusion | Service Due, See Manual |
| Error | Display shows current pump status |
| Battery Depleted | |
| No message on display | |
| Key Pressed, Please Release | |
| No Disposable, Clamp Tubing | |
| No Disposable, Pump Won't Run | |

**Alarms/messages not previously evaluated individually were tested for comprehension in the supplemental study. There were no task failures in responding to all alarms/messages**



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**that are listed in the HCP and patients IFUs by the 15 participants in the supplemental HF study. <u>This response was found acceptable.</u>**

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.
**Summary of Response: AbbVie determined that training more reflective of clinical use (number of sessions and duration) and revisions to the Patient and HCP IFUs would be appropriate actions to mitigate these risks. All revisions made to the IFUs and tested in the supplemental HF study. Results of the Supplemental HF Study showed no task failures in the above scenarios, supporting the adequacy of the mitigations implemented. <u>This response was found acceptable.</u>**

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.
**Summary of Response: Results for the evaluation of patient dose adjustments are provided in the Integrated HF Summary Section 3.2.5. The pump has 2 lock levels for patient use:**

- **lock level 1 (LL1) where the patient can do their own dose adjustment and,**
- **lock level 2 (LL2) where a patient can do no dose adjustments.**

**A patient is assigned to a single lock level by the HCP, based on the HCP evaluation of patient capability to perform their own dose adjustments. The HCP must program the pump (setting the doses) and set the Lock Level (LL1 or LL2) for the individual patient.**
**To evaluate LL1:**

- **Patients and HCPs performed Adjust Morning dose and Adjust Continuous Rate**
- **HCPs demonstrated comprehension of the difference between LL1 and LL2**
- **HCPs performed Pump Programming, setting the lock level**

**The supplemental HF study tested 9 additional HCPs for the critical tasks of programming the pump, including setting the lock level. HCPs used the revised IFUs and the Duopa system to set the pump for patient use. After completing other pump programming tasks, the HCP was asked to set the lock level to LL1 for patient use. All HCP participants completed this critical task successfully. The HCPs were then asked to explain what it meant to the patient to have the pump set in LL1 versus LL2. All HCP participants**



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**successfully described that patients and HCPs can make dose adjustments in LL1 but only HCPs can make dose adjustments in LL2 accordingly. <u>This response was found acceptable.</u>**

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 preprogramming 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.
**Summary of Response: The scenarios in the Lock Level 1 portion of the original HF study described in NDA 203952, May 2013, Module 3, Section 3.2.R, the HF Engineering/Usability Engineering Summary Report for Levodopa-Carbidopa Intestinal Gel Administration System Essential Tasks, were designed to evaluate patients' ability to adjust dose, specifically the continuous rate and morning dose. The LL1 setting allows access to adjust the morning dose, the continuous rate, and the extra dose. In LL2, no dose adjustments are possible by the patient. Only the HCP can reprogram the pump to adjust the dose. In LL1, adjustments can be made by the patient according to the instructions provided in the Patient IFU for the morning dose volume and continuous rate. As noted above, the patient is instructed not to adjust their extra dose volume. Further, the patient cannot adjust the extra dose lockout time. <u>This response was found acceptable.</u>**

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.
**Summary of Response: The task of inspecting the tube for kinks was properly simulated in the primary portion of the original HF study when performing the Morning Dose and Change the Cassette use scenarios, where the g-tube belt was utilized and all 25 patients completed it successfully. One close call was recorded with this task. In the Supplemental HF Study (Section 10.5), all 15 patients and HCPs completed this task successfully. Regarding the confusion expressed by HCPs related to lock levels, the Operator's Manual (HCP IFU) was revised. The single lock level table has been replaced with 2 tables to improve readability and clarify which functions can be performed with each lock level (refer to revised Operator's Manual [HCP IFU]). The revised tables and additional training sessions, which more closely mimicked clinical practice, were used during HCP participant training and available during the supplemental HF study. All HCP participants demonstrated comprehension that patients can make dose adjustments in LL1 but not in LL2.<u>This response was found acceptable.</u>**

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



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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.
**Summary of Response: AbbVie made changes to warning and caution statements in the Patient IFU to optimize the combined instructions by utilizing more simple language. Text was also revised to be more specific to the use of the CADD-Legacy Model 1400 pump with Duopa. The Warnings and Cautions were then prioritized for testing based on risk. As recommended in the CRL, a user group of 15 participants (9 HCPs and 6 patients) were tested for comprehension of the critical warning and caution statements in the Patient IFU. All patients and HCPs successfully interpreted the intended meaning of the warning and caution statements evaluated. This response was found acceptable.**

7. Provide screen shots for the HCP programming tasks and patient dose adjustment tasks.
**Summary of Response: Screen shots for HCP programing tasks and patient dose adjustment tasks have been captured in association with the applicable task in the IFUs and are provided in Appendix B and Appendix C of this response**. **This response was found acceptable.**



Reference ID: 3648488

## Attachment 2: Prior CDRH Human Factors Reviews

APPEARS THIS WAY ON ORIGINAL



Reference ID: 3648488

**DEPARTMENT OF HEALTH AND HUMAN SERVICES** **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

# CDRH Human Factors Consult Review

*** This document contains proprietary information that cannot be released to the public***

DATE: May 8, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Stacy Metz, Regulatory Project Manager, CDER/OND/ODEI/DNP

SUBJECT: **NDA 203952**
Applicant: AbbVie
Drug: Duopa
Device: infusion pump
Intended Use [redacted] (b) (4)
CDRH CTS Tracking: ICC 1400261

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Date: 2014.05.09 09:57:38 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.05.09 10:00:42 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Combination Product Device Information*

**NDA 203952**
Applicant: AbbVie
Drug: Duopa
Device: infusion pump
Intended Use: (b) (4)

### *CDRH Human Factors Involvement History*

- 4/23/2014 – CDRH HF was requested to review the draft human factors validation study protocol. This protocol was submitted as part of type A meeting request to ensure alignment with FDA to address Complete Response decision issued during the last review cycle.
- 5/9/2014 – CDRH HF provided CDER a list of deficiencies to be communicated to the Sponsor.

### *Overview and Recommendation*

The Division of Neurology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a consultative review from CDRH Human Factors team for the human factors validation study protocol for an infusion pump (modified version of the CADD Legacy 1400 pump) to be used with duopa to treat patients with (b) (4)

The supplemental summative study will be conducted with 15 participants— approximately 8 naïve HCPs and 7 naïve patients. Participants will be a mix of Parkinson's disease (PD) patients, and HCPs—e.g., registered nurses and pharmacists. The training for this simulated-test will mimic the intended clinical training. PD participants will perform all critical tasks to simulate normal use of the Duopa system. Responses to all alarms and comprehension of all warning and caution statements will be tested by presenting each PD patient with a smaller subset of each instead. All use failures and close calls will be analyzed to determine if the user interface of the system and associated labeling promotes safe and effective use, or if it requires further risk mitigation.

Review of the supplemental human factors validation study protocol identified several deficiencies that CDRH HF team would like to communicate to AbbVie:

1. Our CR letter requested that you implement mitigations and demonstrate their effectiveness with another human factors study. Your supplemental human factors validation study protocol did not clearly describe the mitigations you are implementing and did not focus on demonstrating their effectiveness. To complete our review, please provide:
    a. Description of all modifications you have made to the device user interface (device design and/or labeling including Instructions for Use, training) and the use



Reference ID: 3648488

specific errors and operational difficulties that were observed in the previous HF study each modification is designed to address; and

b. Explanation of how your protocol, as designed, focuses on evaluating those specific changes such that the data that will be collected can be used to confirm that the changes are effective at reducing the use errors, and do not introduce any new hazards.

2. Your protocol did not include follow-up interview questions for any use errors/failures that users may experience while using the device during simulated use testing. The Agency considers the subjective assessment to be essential and HF/Usability validation testing is considered to be incomplete without it. Please modify your protocol to include direct discussion using open-ended questions for any and all use errors and failures of critical tasks for each test participant. Note that failures should be defined as actions or failure to act that would potentially or inevitably cause a negative clinical impact.

3. Regarding your proposed testing approach to evaluate alarms, warning and caution statements, please test those according to priority rather than a randomized sample, unless alarms, warning, and caution statements are of equal priority. Please provide a prioritized list of alarms and warning and caution statements, and your rationale for the prioritization.

4. Because alarms and warning and caution statements represent critical tasks for users (e.g., detecting, understanding, and taking action/inaction), please submit an abbreviated analysis of use-related risk that includes all user tasks that are associated with them and assess user performance for these in in your supplemental HF study. Your analysis should include potential use errors and associated harm (negative clinical consequences) of each and (as per deficiency #1 above) the risk-mitigation strategies you have applied. You may submit this response by appending/expanding Table 1 of the protocol.

5. The study protocol did not include specific questions for users to discuss their interpretation and response to alarms, warning and caution statements. Please modify your protocol to include assessment of study participant's perspectives on their experience with these critical tasks.

6. To ensure that we are in alignment with your approach for addressing the human factors deficiencies that were identified in the CR letter; we request that you provide a detailed response to each of those deficiencies. To facilitate our review, you are encouraged to submit this response in a table format.



Reference ID: 3648488

## Appendix 1: Summary of Human Factors Study Protocol

The supplemental summative study will be conducted with 15 participants— approximately 8 naïve HCPs and 7 naïve patients. Participants will be a mix of Parkinson's disease (PD) patients, and HCPs—e.g., registered nurses and pharmacists

The training for this simulated-test will mimic the intended clinical training. The planned clinical training will include multiple HCP interactions, particularly for patients during the dose titration stage. The training sessions will include multiple in-person training sessions, a help line users may call, and educational materials that are based on the product IFUs. The sessions will be facilitated by a Certified Nurse Educator (CNE) representing the HCPs who will train users post-approval. A delay period of at least 1 day will take place between the final training session and the testing session to account for the anticipated time lapse between training and testing under normal situations and decay of learning.

PD participants will perform all critical tasks to simulate normal use of the Duopa system.

| Use Scenarios as Described in Patient IFU | Critical Task | Definition of Critical Task Success |
|---|---|---|
| Morning Procedure | Connect the cassette to the pump | Cassette attached completely and without alarm |
| | Connect the pump and cassette to the PEG-J tubing | Connection made to correct port of PEG-J |
| | Start Continuous Rate | Continuous Rate started as indicated by 'Run' on the pump UI |
| | Adjust the Morning Dose in Lock Level 1 | Morning dose lowered or raised as directed by the moderator |
| | Administer Morning Dose | Morning dose given as indicated by 'Morning Dose' and countdown on the pump UI |
| | Adjust the Continuous Rate in Lock Level 1 | Continuous Rate lowered or raised as directed by the moderator |
| Extra Dose | Administer an Extra dose | Extra dose given as indicated by 'Extra Dose' on the pump UI |
| Evening Procedure | Stop a Continuous Rate | Continuous Rate stopped as indicated by pump UI changing from 'Run' to 'Stopped' |
| | Disconnect the pump and cassette from the PEG-J tubing | Cassette tube disconnected from PEG-J tubing |
| | Flush the PEG-J tubing with water using a syringe | J tube port flushed with water |
| | Disconnect the cassette to the pump | Cassette detached |
| Alarms and Messages Warnings and Cautions | Respond to pump alarm messages | Comprehension of alarm message and identification of appropriate next step to resolve alarm or seek additional help |
| | Comprehension of warnings and cautions statements for critical tasks | Identification of intended meaning of the stated message |

HCPs will complete two other critical tasks, in addition to completing the above patient critical tasks.

| Use Scenarios as Described in Operator's Manual | Critical Task | Critical Task Success |
|---|---|---|
| Pump Programming Quick Reference for Healthcare Providers | Program the pump for patient use | Settings entered into pump identical to information moderator provides to the HCP. Moderator to review pump settings post-performance. |
| | Set pump to Lock Level 1 or Lock Level 2 | HCP identifies understanding of appropriate patient for LL1 and appropriate patient for LL2. Completes pump setting per moderator request for LL1 or LL2. Moderator to review pump settings post-performance. |



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Responses to all alarms and comprehension of all warning and caution statements will be tested by presenting each PD patient with a smaller subset of each instead. For example, there are 12 alarms identified in the patient IFU. Alarms will be tested by showing each participant a smaller and random selection of 4 to 5 pump screens of an alarm message on a flashcard. Participants will be asked questions to determine their comprehension of the alarm message and the appropriate response to resolve the alarm. Similarly, there are numerous warning and caution statements. Each statement will be evaluated for patient comprehension, but not all statements will be evaluated by each patient in every test session.

All use failures and close calls will be analyzed to determine if the user interface of the system and associated labeling promotes safe and effective use, or if it requires further risk mitigation.



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## Appendix 2: CDRH HF Deficiencies (included in the CR letter)

Your human factors study report did not provide analyses and results consistent with best practice to support review of human factors for your combination product submission. As per 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, HCPs and patients combined to demonstrate their effectiveness.

1. Only low battery and high pressure alarms were tested 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 pump labeling that were not part of the study. If the response and interpretation to these alarms/messages is unique and represent critical user tasks, they should be tested but were not tested in your human factors validation study. Unless there are no critical user tasks associated with these alarms and messages, please include them in your human factors testing of mitigations.
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/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. Therefore, please 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. Please provide test results for these tasks or provide justification for the study methodology you followed. Please also clarify the specific patient characteristics for HCPs' determination 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 patient's 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). Please 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.



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5. Your supplemental study results showed six (6/15) patients failed to inspect for tubing kinks prior to programing 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, please 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 statements that have were not included in your human factors testing. Interpreting and abiding by warnings is considered to represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings could lead to patient harm. Please ensure that these instructions are optimized for safe and effective use, and that they are not simply a combination of two instructions.
7. Please provide screen shots for the HCP programming tasks, and patient dose adjustment tasks.



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**DEPARTMENT OF HEALTH AND HUMAN SERVICES** **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

# CDRH Human Factors Review

DATE: February 24, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Gerald Podskalny, Medical Officer, CDER/OND/ODEI/DNP
Stacy Metz, Regulatory Project Manager, CDER/OND/ODEI/DNP

SUBJECT: **NDA 203952**
Applicant: AbbVie Inc.
Device Constituent: Infusion Pump
Drug Constituent: Levodopa/Carbidopa Intestinal Gel
Intended Treatment: Parkinson's disease
CDRH CTS Tracking No.: ICC 1300534

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Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.03.06 08:55:54 -05'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.03.07 16:25:01 -05'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Combination Product Device Information*

Submission No. NDA 203952
Applicant: AbbVie Inc.
Device Constituent: Infusion Pump
Drug Constituent: Levodopa/Carbidopa Intestinal Gel
Intended Treatment: Parkinson's disease

### *CDRH Human Factors Involvement History*

- 6/4/2013 – CDRH HF was requested to review the human factors validation study report included in the NDA. Review Materials:
  EDR Location: \\CDSESUB1\EVSPROD\NDA203952\203952.enx
- 12/23/2013 – CDRH HF provided information requests to obtain clarification and additional information

### *Overview and Recommendation*

The Division of Neurology Products, Office of Drug Evaluation II, Office of New Drugs, requested the CDRH Human Factors (HF) team to review human factors validation study report contained in the NDA. The device constituent is an infusion pump and it is used to administer Levodopa-carbidopa intestinal gel, which is indicated for long term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)

Prior to submitting the NDA, AbbVie submitted a human factors study report in IND 60663. CDRH HF was consulted to review the report and provide comments. At the time, CDRH HF identified four deficiencies including a request for Abbvie to further optimize the device, and to perform a focused HF/usability validation study demonstrating that representative users can use the device without patterns of preventable use errors/failures that can result in patient harm. These deficiencies were provided to CDER on 8/29/2012. Subsequently, AbbVie requested to have a teleconference with CDRH HF review to obtain clarifications on the deficiencies, and to ensure Abbvie understands the reviewer's expectations for reviewing the report that will be contained in the NDA. With CDER's concurrence, the teleconference was held on 9/17/2012 with representatives from CDRH HF team, and AbbVie. AbbVie was advised to provide the following in their final report:

- Further elaboration is needed on what happened after task failures, and the possible clinical impact of these user actions, and if needed, a discussion of what could be changed in the user interface to address those failures
- Further discussion on test results of the alarm tasks
- Further discussion on lock level functions and capabilities. CDRH HF team recommended that to assess user's ability to operate the different lock levels (amount of user access) additional HF testing should be conducted with at least 15 representative users.



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The study report submitted in the NDA is an updated report that included elaboration on task failures and discussion of alarms tested. In addition, the study report also included a supplemental human factors test results for assessing physician's knowledge on the differences between the four lock levels, and assessing patients' ability to adjust dose for lock level 1. Review of this identified several concerns regarding the study methodology and results. It should be noted that the overall product instructions for use and the pump patient information were combined based on FDA's recommendation. The resulting instructions for use for patients have warnings and caution statements that have not been tested with representative patients. A detailed review of the study report can be found in Appendix 1.

At this time, the consultant recommends communicating the following deficiencies to the Sponsor:

Your human factors study report did not provide analyses and results consistent with best practice to support review of human factors for your combination product submission. As per 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, HCPs and patients combined to demonstrate their effectiveness.

1. Only low battery and high pressure alarms were tested 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 pump labeling that were not part of the study. If the response and interpretation to these alarms/messages is unique and represent critical user tasks, they should be tested but were not tested in your human factors validation study. Unless there are no critical user tasks associated with these alarms and messages, please include them in your human factors testing of mitigations.
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/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. Therefore, please 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. Please provide test results for these tasks or provide justification for the study methodology you followed. Please



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also clarify the specific patient characteristics for HCPs' determination 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 patient's 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). Please 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 programing 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, please 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 statements that have were not included in your human factors testing. Interpreting and abiding by warnings is considered to represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings could lead to patient harm. Please ensure that these instructions are optimized for safe and effective use, and that they are not simply a combination of two instructions.
7. Please provide screen shots for the HCP programming tasks, and patient dose adjustment tasks.



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## Appendix 1: CDRH Human Factors Review

AbbVie conducted two human factors validation tests with representative users in a simulated use study. The device constituent consists of a portable/wearable drug delivery system that is used to deliver the drug product Levodopa/Carbidopa Intestinal Gel (LCIG). The delivery system consists of an ambulatory infusion pump that delivers continuous LCIG from a medication cassette, and a percutaneous endospcopic gastrostomy with jejunal tube system (PEG-J) that delivers the drug to the upper jejunum from long term LCIG treatment.

Healthcare providers (HCPs) are expected to set up and program the infusion pump prior to providing the pump to the patients. The infusion pump offers three lock levels:

- Lock Level 0 (LL0): this lock level is reserved for only HCPs to make dose changes (bolus dose [morning dose], continuous flow rate, or extra dose) during initial titration. This lock level requires a code to change out the lockout times for the morning, and extra dose.
- Lock Level 1 (LL1): this lock level can be accessed by patients. The patients are enabled to adjust the dose between a preset prescribed dose and a pre-programming upper limit (+10% of the prescribed dose). The default lock out time for the morning dose is 20 hours.
- Lock Level 2 (LL2): No dose changes can be made by patients.

AbbVie expects that every user will receive comprehensive training on how to use the delivery system prior to first use. The training provided in the study represented "the worst-case" training. AbbVie stated that there are no safety critical tasks (i.e. those that would result in death, serious/permanent injury or disability to the user) based on their risk analysis. However, the consultant remains concerned that the study results (both original and supplemental) described task failures and use errors that could result in patient harm. In addition, the consultant has some concerns associated with the study methodology both original and supplemental studies. These concerns are outlined below:

1. **Original HF study**
    a. Concerns about methodology
        i. Only low battery and high pressure alarms were tested but not in the naturalistic occurrence of these alarms. Also, there are other alarms (listed in the HCPs and Patients pump labeling), if response/interpretation to these alarms is unique, they should have been tested in the study.
    b. Concerns about results
        i. HCPs experienced programming failures and close calls that could result in overdose/underdose
            1. One HCP accidentally changed Continuous Rate value while changing Morning Dose volume. HCP realized that she input the wrong value but did not correct it. HCP expressed confusion of Morning Dose volume versus Continuous Rate value. Review of HCP operator manual for Morning Dose programming steps did not clarify how Continuous Rate value would appear during the programing sequence for Morning Dose. However, the study report



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did not include subjective data describing what aspect of the device user interface caused the HCP to be confused, and how that could have been improved from the HCP's perspective. There was no quantitative data on how much of an overdose that would have result, % of rate change, and the magnitude of the error was not characterized.

2. 2 HCPs failed to administer Morning Dose, which could have resulted in an underdose. HCPs were required to press Morning Dose button twice to initiate delivery. However, HCPs misinterpreted pump user interface display "RUN" to indicate that the pump was administering the Morning Dose. Review of the HCP operator manual indicated that the need to press the button twice was not emphasized. In addition, the programing sequence for the Morning Dose did not seem to include the pump display the word "RUN." In addition, the reviewer is unclear which specific instances where the pump would display the word "RUN" in all HCP programming tasks.

ii. HCPs and patients experienced failures in connecting device components

1. 5/25 HCPs and 14/25 patients experienced failures with critical tasks associated with changing the cassette. Most notably, users failed to remove the red cap from the cassette tubing before connecting it to the stomach tubing, which can result in medication not being delivered. Two patients flushed the tubes inappropriately, which would result in an immediate dose followed by a delayed dose, and can disrupt Continuous Rate flow. User interviewed data were not provided to assess possible root cause.
2. 3 patients and 6 HCPs did not complete the steps for flushing the PEG-J tubing, which could result in medication not being delivered. User interviewed data were not provided to assess possible root cause.

c. No evidence demonstrating that mitigations are effective

i. Incorrect programming will be caught and proper setting will be programmed during patient titrations. The consultant is unclear how and where patient titration would take place. The study report did not include a scenario where users recognize programming errors, and take appropriate actions to correct them.

ii. Patient will recognize reemergence of symptoms, and that a dose has not been delivered, and would be able to deliver an Extra Dose. However, the study report did not include a scenario where users would understand the need to deliver an Extra Dose and perform the necessary user steps associated with delivery an Extra Dose.

**2. Supplemental Study**

a. Concerns about methodology:

i. 10 HCPs were not tested in going through the steps of setting up lock levels. The consultant is unclear which patients would be elected to



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receive a pump with LL1 versus patients with LL2 pump. The consultant is unclear if specific patient characteristics eligible for LL1 be described in labeling and/or a patient competency checklist should be developed for HCPs.

ii. 15 patients were tested to perform Morning Dose and Continuous Rate adjustments. The consultant is unclear circumstances for which patients would need to adjust dose and how much adjustments can made relative to the prescribed dose for individual patients.

b. Concerns about results

i. 6/15 patients did not inspect for tubing kinks prior to programing adjustments, which was considered to be critical task.

ii. HCPs indicated some confusion regarding the table in the HCP pump labeling that describes the functionalities associated with the different lock levels and whether Morning Dose could be adjusted in LL1.

**3. Combined instructions for patients and implications for additional HF studies**

a. Introduction of warnings and cautions, which are critical knowledge tasks that users need to understand and follow

b. The consultant needs to review evidence demonstrating that users can perform those critical tasks



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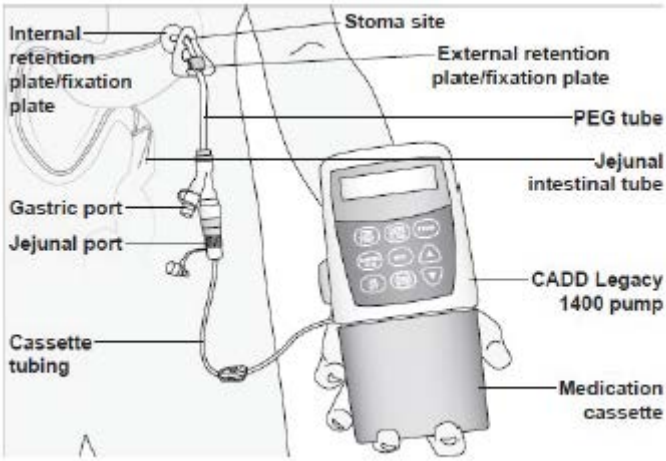
## Appendix 2: Device Related Information

The LCIG Administration System includes a software-driven, ambulatory infusion pump with accessories and a variety of enteral tubing products, including a jejunal tube inserted through a percutaneous endoscopic gastrostomy port (PEG-J) and a naso-jejunal (NJ) tube to be used for an optional initial phase.




Each morning, after attaching the pump, cassette and tubing, the user powers on the pump and initiates a bolus dose called a Morning Dose, which primes the tubing and delivers a bolus infusion of LCIG. After the Morning Dose delivery, the pump automatically transitions to a constant basal dose called the Continuous Rate. At any point during
Continuous Rate delivery, the user can initiate another bolus dose called an Extra Dose. Extra Dose availability and amount is prescribed by the user's physician and then programmed into the pump by the physician or other HCP. At the end of the day, the user disconnects the LCIG Administration System's components, stores the pump, discards the cassette and flushes the port of the PEG-J tubing with potable water. The LCIG drug product is stored under refrigerated conditions and can be used for up to 16 hours at room temperature.



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

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/s/

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TRACY J PETERS
10/27/2014

# REGULATORY PROJECT MANAGER
# PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
# OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 203952

**Application Type:** New NDA (resubmission)

**Name of Drug/Dosage Form:** Duopa
Carbidopa and Levodopa Enteral Suspension
[formerly stated as Levodopa Carbidopa Intestinal Gel (LCIG)]

**Applicant:** AbbVie

**Receipt Date:** July 11, 2014

**Goal Date:** January 11, 2015

## 1. Regulatory History and Applicant's Main Proposals

Duopa is delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). The proposed indication is "for the long-term treatment of motor fluctuations in patients with advanced Parkinson's disease".

The original application was submitted on November 16, 2012, to which a Refuse to File (RTF) letter was issued on January 15, 2013. The NDA was resubmitted after the RTF on May 28, 2013, and a SRPI review was conducted on the labeling provided in that submission. Labeling deficiencies were identified, as stated in the March 28, 2014 review conducted by Stacy Metz. It was determined that the application could not be approved at that time, and on March 28, 2014, a Complete Response letter was issued. On July 11, 2014, a Class 2 resubmission was received for the NDA. This SRPI review is based on the labeling that was provided by the applicant in that resubmission.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.



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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

# Highlights

**See Appendix A for a sample tool illustrating the format for the Highlights.**

**HIGHLIGHTS GENERAL FORMAT**

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

***Comment:*** *Less than a half inch margin on the left when printed and measured*

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

***Comment:*** *Waiver over half-page--Waiver request submitted in 5/28/14 submission*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

***Comment:***

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

***Comment:***

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

***Comment:***

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

***Comment:***

YES 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|---|---|
| ! **Highlights Heading** | Required |
| ! **Highlights Limitation Statement** | Required |
| ! **Product Title** | Required |



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# Selected Requirements of Prescribing Information

| | |
|---|---|
| ! **Initial U.S. Approval** | Required |
| ! **Boxed Warning** | Required if a BOXED WARNING is in the FPI |
| ! **Recent Major Changes** | Required for only certain changes to PI* |
| ! **Indications and Usage** | Required |
| ! **Dosage and Administration** | Required |
| ! **Dosage Forms and Strengths** | Required |
| ! **Contraindications** | Required (if no contraindications must state "None.") |
| ! **Warnings and Precautions** | Not required by regulation, but should be present |
| ! **Adverse Reactions** | Required |
| ! **Drug Interactions** | Optional |
| ! **Use in Specific Populations** | Optional |
| ! **Patient Counseling Information Statement** | Required |
| ! **Revision Date** | Required |

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

***Comment:***

## HIGHLIGHTS DETAILS

### Highlights Heading

**YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

***Comment:***

### Highlights Limitation Statement

**YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

***Comment:***

### Product Title in Highlights

**YES** 10. Product title must be **bolded**.

***Comment:***

### Initial U.S. Approval in Highlights

**YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

***Comment:***

### Boxed Warning (BW) in Highlights

**N/A** 12. All text in the BW must be **bolded**.

***Comment:***

**N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.



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***Comment:***

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

***Comment:***

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

***Comment:***

**Recent Major Changes (RMC) in Highlights**

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

***Comment:***

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

***Comment:***

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

***Comment:***

**Indications and Usage in Highlights**

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

***Comment:*** *As stated in Sinemet PI: Carbidopa is an inhibitor of aromatic amino acid decarboxylation and Levodopa is an aromatic amino acid*

**Dosage Forms and Strengths in Highlights**

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

***Comment:***

**Contraindications in Highlights**



Reference ID: 3639192

**YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

***Comment:*** *Melanoma is not listed under contraindications for Sinemet*

**Adverse Reactions in Highlights**

**YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

***Comment:***

**Patient Counseling Information Statement in Highlights**

**NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

! **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

! **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**

! **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

***Comment:*** *Submitted patient IFU also, therefore, should be "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"*

**Revision Date in Highlights**

**YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

***Comment:*** *Use single number month, depending on approval date*



Reference ID: 3639192

# Contents: Table of Contents (TOC)

**See Appendix A for a sample tool illustrating the format for the Table of Contents.**

**YES** 25. The TOC should be in a two-column format.

***Comment:***

**YES** 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

***Comment:***

**N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

***Comment:***

**YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

***Comment:***

**YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

***Comment:***

**YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

***Comment:***

**YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

***Comment:***



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# Full Prescribing Information (FPI)

## FULL PRESCRIBING INFORMATION: GENERAL FORMAT

**YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|---|
| **BOXED WARNING** |
| **1 INDICATIONS AND USAGE** |
| **2 DOSAGE AND ADMINISTRATION** |
| **3 DOSAGE FORMS AND STRENGTHS** |
| **4 CONTRAINDICATIONS** |
| **5 WARNINGS AND PRECAUTIONS** |
| **6 ADVERSE REACTIONS** |
| **7 DRUG INTERACTIONS** |
| **8 USE IN SPECIFIC POPULATIONS** |
| **8.1 Pregnancy** |
| **8.2 Labor and Delivery** |
| **8.3 Nursing Mothers** |
| **8.4 Pediatric Use** |
| **8.5 Geriatric Use** |
| **9 DRUG ABUSE AND DEPENDENCE** |
| **9.1 Controlled Substance** |
| **9.2 Abuse** |
| **9.3 Dependence** |
| **10 OVERDOSAGE** |
| **11 DESCRIPTION** |
| **12 CLINICAL PHARMACOLOGY** |
| **12.1 Mechanism of Action** |
| **12.2 Pharmacodynamics** |
| **12.3 Pharmacokinetics** |
| **12.4 Microbiology (by guidance)** |
| **12.5 Pharmacogenomics (by guidance)** |
| **13 NONCLINICAL TOXICOLOGY** |
| **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** |
| **13.2 Animal Toxicology and/or Pharmacology** |
| **14 CLINICAL STUDIES** |
| **15 REFERENCES** |
| **16 HOW SUPPLIED/STORAGE AND HANDLING** |
| **17 PATIENT COUNSELING INFORMATION** |

***Comment:*** *Remove "class" from 9.1 subheading*

**NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".



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***Comment:*** *In section 2.1 and 5, statements with simply "in Section X" rather than the proper cross-reference bracket format. Incorrect format in 7.2.*

**N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

**FULL PRESCRIBING INFORMATION DETAILS**

**FPI Heading**

**YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

***Comment:***

**BOXED WARNING Section in the FPI**

**N/A** 36. In the BW, all text should be **bolded**.

***Comment:***

**N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

***Comment:***

**CONTRAINDICATIONS Section in the FPI**

**N/A** 38. If no Contraindications are known, this section must state "None."

***Comment:***

**ADVERSE REACTIONS Section in the FPI**

**YES** 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

***Comment:*** *Applicant added "…of another drug (or of another development program of a different formulation of the same drug)…"*

**YES** 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

***Comment:*** *Foreign marketing as Duodopa.*



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# Selected Requirements of Prescribing Information

**PATIENT COUNSELING INFORMATION Section in the FPI**

**YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

***Comment:***

**YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

***Comment:*** *Not included as subsection; will attach at approval*



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## Appendix A: Format of the Highlights and Table of Contents

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].**

**[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]**
**Initial U.S. Approval: [year]**

**WARNING: [SUBJECT OF WARNING]**
***See full prescribing information for complete boxed warning.***

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

**To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

**See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].**

**Revised: [m/year]**

---

**FULL PRESCRIBING INFORMATION: CONTENTS***


WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION


*Sections or subsections omitted from the full prescribing information are not listed.

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Reference ID: 3639192

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

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/s/

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TRACY J PETERS
10/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

**Date:** February 27, 2014

**From:** CDR Alan Stevens, Reliability and Mechanical Engineering
Infusion Pump Team Leader, OMPT/CDRH/ODE/DAGRID/GHDB

**To:** Stacy Metz, Senior Regulatory Health Project Manager,
OMPT/CDER/OND/ODEI/DNP

**Subject:** CDRH Consult for NDA 203952, infusion pump for enteral delivery of Levodopa / Carbidopa Intestinal Gel

Device Sponsor: Smiths Medical
Device Name: CADD Legacy 1400 Pump System

# I. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203952. The device constituent of this combination product consists of an infusion pump system.

# II. Documents

Documentation for the infusion pump is contained in device master file, MAF (b) (4) Amendment 3.

# III. Review

Indications for Use

| Product | Indications for Use |
|---|---|
| CADD 1400 Legacy Pump System | The CADD-Legacy 1400 Pump is indicated solely for enteral delivery of medication contained in a medication cassette reservoir supplied by AbbVie. The medication cassette reservoir attaches to the bottom of the pump. |
| Levodopa / Carbidopa Intestinal Gel | Levodopa-carbidopa intestinal gel is a combination of levodopa and carbidopa, indicated for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4) |

Device Description
The CADD-Legacy 1400 Pump System (hereinafter referred to as "CADD-Legacy" or "the pump") is a modification to the existing FDA Cleared CADD-Legacy PCA Pump System (K982839) and Medication Cassette Reservoir (K846772). The CADD-Legacy 1400 Pump System was developed as a specific enteral medication system and will not be indicated for enteral feeding applications. Prior to launching the CADD-Legacy 1400 Pump System, changes were made to the CADD-Legacy PCA System (b) (4)

(b) (4) as described in TAB 7 of MAF (b) (4) Amendment 3), labeling, and software to modify features and capabilities that address the needs for enteral delivery of medication. The CADD-Legacy 1400 Pump is supplied with the following accessories:

- Remote Dose Cord
- Pump Pouch
- Protective Cassette
- Battery Door

All four accessories have been cleared in other 510(k) submissions. Refer to Table 3-1 below for the matrix of accessories and associated 510(k)s.

**Table 3-1.** List of CADD-Legacy® 1400 Pump accessories and Cleared 510(k)s.

| Description | Product Code(s) | 510(k) |
|---|---|---|
| CADD-Legacy® Remote Dose Cord | 21-6220 | K982839 |
| CADD-Legacy® Pump Pouch, Single Use, 50/100 mL, 10-pack | 21-2170[1] | K982839 |
| CADD-Legacy® Battery Door | 21-6216 | K982839 |
| Pump Admin Set Housing, Protector | 21-6235 | K982839 |

The CADD-Legacy 1400 Pump will be used with a custom enteral Medication Cassette Reservoir and the CADD-Legacy 1400 Pump will be supplied non-sterile. A red warning flag has been added to the extension tube to warn against intravenous connection of the Medication Cassette Reservoir. This Medication Cassette Reservoir, product code 21-7110, has not been part of a 510(k) submission. It is the subject of Drug Master File DMF- (b) (4)

While the CADD-Legacy® 1400 Pump may be used in the hospital, its primary intended use is in the alternate site environment - including but not exclusive to treatment of patients in their homes, institutional care centers, or physician offices.

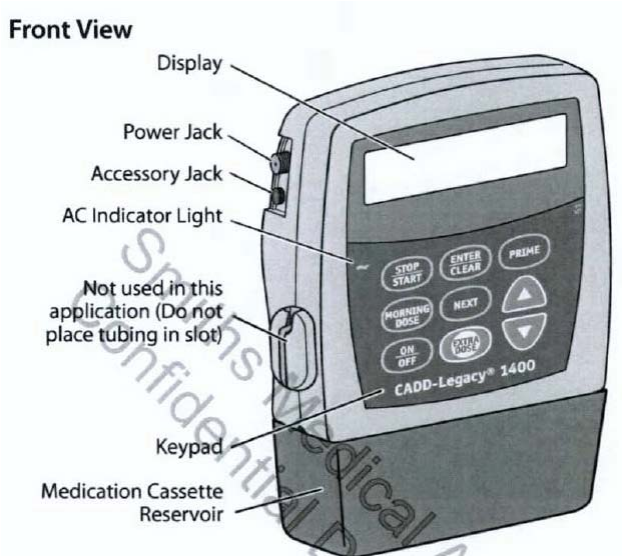
The CADD-Legacy 1400 Pump consists of the following major components: user interface, sensors, power port, structural components, electronics, pumping mechanism, watchdog timer, pump battery and circuitry, real time clock (RTC), on-board memory, and accessories.

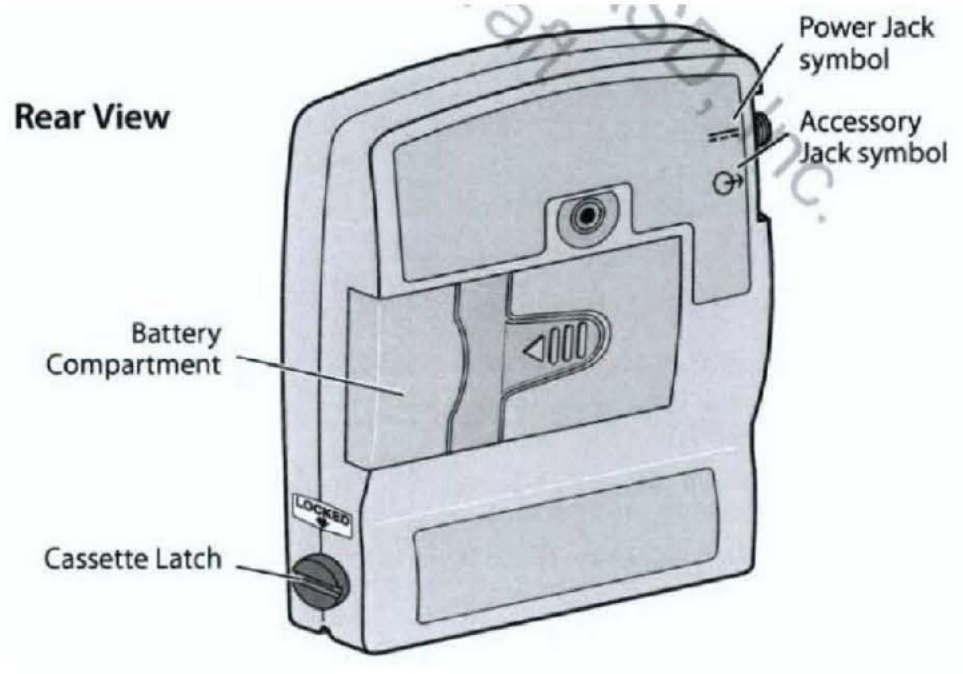
User Interface

A picture of the device user interface is provided below and the table includes a brief description for the function of each key.

| Name of Key | Description of Use |
|---|---|
| STOP/START | The STOP/START key is used to transition the pump from the STOP mode to the RUN mode or form the RUN mode to the STOP mode. Additionally, pressing this key will acknowledge and cancel some alarms. Pressing the STOP/START key triggers this function. |
| ENTER/CLEAR | The ENTER/CLEAR key is used to save an edited value or clear the value of a variable associated with the currently displayed screen. Pressing the ENTER/CLEAR key triggers this function. |

| | |
|---|---|
| PRIME | The PRIME key is used to deliver a controlled amount of fluid during STOP mode in order to help remove air from the disposable reservoir and tubing. Pressing the PRIME key triggers this function. |
| NEXT | The NEXT key will generally be used for navigation between screens and to acknowledge alarms. Additionally, pressing this key will both acknowledge and cancel the alarm. Pressing the NEXT key triggers this function. |
| UP ARROW | The Up Arrow key is used to increase the value of a variable associated with the currently displayed screen when in EDIT mode. Pressing the Up Arrow key triggers this function. |
| DOWN ARROW | The Down Arrow key is used to decrease the value of a variable associated with the currently displayed screen when in EDIT mode. Pressing the Down Arrow key triggers this function. |
| ON/OFF | The ON/OFF key is used to put the pump into a low power state when not in use. Pressing the ON/OFF key triggers this function. |
| EXTRA DOSE | The EXTRA DOSE key is used to implement the demand (or "extra") dose feature. When this key is pressed in the RUN Mode, the pump initiates processing for the extra dose. |
| MORNING DOSE | The MORNING DOSE key is used to implement the loading bolus (or "morning dose") feature. When this key is pressed in the RUN Mode, the pump initiates processing for the morning dose. |
| Remote Dose Cord | The Remote Dose Cord is used to remotely implement the morning dose and extra dose features. When the button on the Remote Dose Cord is pressed while the CADD-Legacy® 1400 Pump is in RUN Mode, the pump initiates processing for the morning dose or extra dose. |




Rear View
Power Jack symbol
Accessory Jack symbol
Battery Compartment
LOCKED
Cassette Latch

Sensors

The infusion pump includes three sensors in the design for detecting hazardous situations. The sensor name and a description of its purpose are identified in the following table:

| Sensor Name | Description of Use |
|---|---|
| Upstream Occlusion Sensor | Detects upstream occlusions in the infusion line of the Medication Cassette Reservoir prior to reaching the pumping mechanism. |
| Downstream Occlusion Sensor | Detects downstream occlusions in the infusion line, which occur downstream of the pumping mechanism. |
| Medication Cassette Reservoir Detection Sensor | Detects if there is a Medication Cassette Reservoir properly attached |

Structural Components
The main structure for the CADD-Legacy' 1400 Pump consists of a front and rear housing enclosing the microprocessor and printed circuit board, display and pumping mechanism; battery compartment and a cassette latch assembly.

Electronics
The CADD-Legacy" 1400 Pump contains a microprocessor and other circuitry which control the CADD-Legacy' 1400 Pump. The microprocessor and circuitry are located on a printed circuit board. The board contains the Central Processing Unit (CPU), motor driver circuitry, and other circuitry. The circuitry is designed to reduce the susceptibility to interference from electromagnetic fields and to dissipate electrostatic discharge.

Pumping Mechanism
The pumping mechanism of the CADD-Legacy 1400 Pump is [redacted] (b) (4)

Pumping Mechanism Sequence
[redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

Power Requirements
Power for the CADD-Legacy® 1400 Pump is supplied by two "AA" alkaline batteries. The CADD-Legacy 1400 Pump has been designed to accommodate two (2) batteries that mechanically conform to NEDA/ANSI standard 15A or IEC LR6 (type "AA"). This is identical to the CADD-Legacy PCA Pump. The CADD-Legacy 1400 Pump is also capable of being powered with an AC adapter, although an AC adapter is not being supported for the CADD-Legacy 1400 Pump.

The expected life of two (2) "AA" batteries is 100 hours at 100 ml/16 hours, or approximately fourteen (14) days at ten (10) ml/day (nominal). This estimate is based on laboratory tests conducted at room temperature using two (2) new batteries. Actual battery life will vary depending on the brand of battery, battery shelf life, temperature conditions, and delivery rate. An internal battery powers the clock. The internal battery has an expected life of five (5) years and is replaced by Smiths Medical.

Operational Specifications and Descriptions

| Characteristic | Specification |
|---|---|
| System Infusion Delivery Accuracy | (b) (4) % (nominal) |
| Bolus Delivery Accuracy | % |
| Flow Rates | 0mL/hr to 20 mL/hr<br>It can be set in 0.1 mL/hr increments. |
| Size | 4.1cm x 9.5cm x 11.2cm, excluding cassette |
| Weight | 392 gram, including 2 AA batteries and empty 100 mL CADD medication cassette reservoir. |
| Fluid Ingress Protection | Splashproof (IPX4) |
| Pump Alarms | Low battery<br>Depleted battery<br>Battery dislodged<br>Pump stopped<br>Pump fault<br>Low reservoir volume<br>High delivery pressure<br>Air in line<br>Disposable not attached when run attempted<br>Motor locked<br>Upstream occlusion<br>Downstream occlusion<br>Reservoir volume empty<br>Program incomplete<br>Remote dose cord removed<br>Key stuck<br>Disposable detached |
| Maximum infusion pressure | 40 psi |
| Time to Occlusion Alarm | Infusion rate \| Time to Occlusion Detection<br>(b) (4) |

| | |
|---|---|
| | (b) (4) [redacted] |
| Bolus Volume at Occlusion Alarm | Infusion rate: Bolus Volume at Occlusion Alarm<br>(b) (4) [redacted] |
| System Operating Temperature | 2 C to 40 C (35 F to 104 F) |
| System Storage and Transportation Temperature | -20 C to 60 C (-4 F to 140 F) |
| High Pressure Alarm | 26 ± 14 psi |
| [redacted] (b) (4) | |
| Maximum Volume Infused under Single Fault Condition | 0.2mL |

# Safety Engineering Review

**Safety Assurance Case – Introduction**

Given that safety is a system property that cannot be directly measured an argument is required to convince a qualified reviewer that adequate safety has been achieved.

A safety assurance case consists of a structured argument, supported by a body of evidence that provides a compelling, comprehensible and valid case that a medical device is safe for its intended use (e.g. for use on intended patient populations, by intended users, within intended environments of use).

Safety assurance cases (or safety case) are unique to individual products and are dependent on individual product requirements, hazards, design, and documentation and the safety case methodology is fundamentally grounded in safety engineering practice and principles. CDRH began piloting the use of safety cases for infusion pumps in April 2010 in response to increased numbers of infusion pump recalls.

**Review of Adverse Events and Recalls**

I conducted a review of CDRH's adverse event and recall database for issues related to the CADD-Legacy system.

The top reported adverse events are related to leaking of the medication cassette, air bubbles in the cassette, and occluded cassettes.

A corresponding Class II recall (Z-0876-2008) to address the leaking cassettes was opened in 2007 and terminated in 2008.

Issues related to air bubble formation and occlusion will be investigated throughout the review of the device safety case.

**Safety Assurance Case – Review**

Smiths Medical has provided a safety case for the CADD-Legacy 1400 infusion pump.

The primary argument I am interested in to assure an adequately safe design is identified as Argument A110 in the safety case:

*A110: Because all hazards to safety and their associated failure modes and causes have been identified.*

Hazards are categorized by Smiths Medical:

- Under / Over Delivery of Fluid
- Delay of Therapy
- Incorrect Therapy
- Over Pressure
- Infection
- Allergic Response
- Trauma / User Injury
- Excessive Heat or Fire
- Electric Shock or Excessive Patient Leakage Current
- Risks to Environment

This device platform is based on a cleared device and many of the hazards have been addressed in the device system for general use, such as electrical safety, environmental hazards, trauma, sterility, and allergic response. For purposes of this review, I am going to focus on Infusion Delivery Error hazards. This category includes under delivery, over delivery, and delay of therapy hazards.

The hazard analysis assumes 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.

**Infusion Delivery Error.**

**I have conducted a complete review of the hazards analysis documentation (MAF (b) (4) Amendment 3, VOL 6 TAB 10B CADD Legacy 1400 Pump Hazard Analysis) provided for the CADD Legacy 1400 system. I have recorded deficiencies in the analysis in the following table.**

| **Hazard** | | |
|---|---|---|
| Infusion delivery occurs at an incorrect rate | | |
| **Cause** | **Control** | **Deficiency** |
| (b) (4) | | |

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

(b) (4)

[redacted]

## IV. Recommended Deficiencies

Complete Review Deficiencies

1. Please 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 [redacted] (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 [redacted] (b) (4) respectively. Please clarify the correct accuracy specifications.

    b. The design verification report (DVT-1258R-000) states that the Dose Volume accuracy specification should be updated to [redacted] (b) (4)

(b) (4) It is not clear if this recommendation was followed. Please 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, cassette, tubing configuration, drug temperature, etc.

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. Please 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 re-tested and that no new anomalies are 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.

3. 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 identifies the 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). Column 3 identifies additional information needed to complete our review. Please address the deficiencies identified in column 3.

| **Hazard** - Infusion delivery occurs at an incorrect rate | | |
|---|---|---|
| **Cause** | **Control** | **Deficiency** |

(b) (4)

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

(b) (4)

[redacted]

Review Issues

4. Drug labeling indicates that neuroleptic malignant syndrome (NMS) is associated with abruptly reduced / discontinued drug dosage or therapy. 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. What timeframe is required for onset of NMS and how are device malfunctions adequately handled to reduce the risk of NMS onset.

b. With respect to occlusion detection, the system specifications provide the time to occlusion detection. Verify that these times are acceptable to mitigate harm from NMS.
c. 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 specification time-to-detection are derived from the design verification tests using LCIG.
d. The occlusion detection alarm specification is 26psi +/-14psi. Describe is 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.

5. There appears 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 Gel.

6. 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.

7. (b) (4)

## V. Decision Recommendation

I recommend conveying the deficiencies to the sponsor. The Complete Review deficiencies need to be resolved prior to approval.

| Digital Signature Concurrence Table | | |
|---|---|---|
| Reviewer | Alan M. Stevens -S | Date: 2014.02.27 12:46:47 -05'00' |
| Supervisor | | Digitally signed by Richard C. Chapman Date: 2014.02.27 12:52:07 -05'00' |

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

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/s/

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STACY M METZ
03/28/2014

# RPM FILING REVIEW

**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

| Application Information | | |
|---|---|---|
| NDA # 203952<br>BLA# | NDA Supplement #:S-<br>BLA STN # | Efficacy Supplement Type SE- |
| Proprietary Name: Duopa<br>Established/Proper Name: Levodopa Carbidopa Intestinal Gel<br>Dosage Form: Intestinal Gel<br>Strengths: 20 mg/mL, 5 mg/mL | | |
| Applicant: AbbVie<br>Agent for Applicant (if applicable): Matt Kuntz | | |
| Date of Application: May 28, 2013<br>Date of Receipt: May 28, 2013<br>Date clock started after UN: | | |
| PDUFA Goal Date: March 28, 2014 | Action Goal Date (if different): | |
| Filing Date: July 27, 2013 | Date of Filing Meeting: July 1, 2013 | |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3 | | |
| Proposed indication(s)/Proposed change(s): Long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease [redacted] (b) (4) | | |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:<br><br>***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:***<br>***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html***<br>***and refer to Appendix A for further information.*** | ☐ 505(b)(1)<br>☒ 505(b)(2)<br>☐ 505(b)(1)<br>☐ 505(b)(2) | |
| Review Classification:<br><br>***If the application includes a complete response to pediatric WR, review classification is Priority.***<br><br>***If a tropical disease priority review voucher was submitted, review classification is Priority.*** | ☒ Standard<br>☐ Priority<br><br>☐ Tropical Disease Priority Review Voucher submitted | |
| Part 3 Combination Product? ☒<br>***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults*** | ☐ Drug/Biologic<br>☒ Drug/Device<br>☐ Biologic/Device | |
| ☐ Fast Track<br>☐ Rolling Review<br>☒ Orphan Designation<br><br>☐ Rx-to-OTC switch, Full<br>☐ Rx-to-OTC switch, Partial<br>☐ Direct-to-OTC<br><br>Other: | ☐ PMC response<br>☐ PMR response:<br>☐ FDAAA [505(o)]<br>☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br>☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br>☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | |



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| | | |
|---|---|---|
| Resubmission after withdrawal? ☐ | Resubmission after refuse to file? ☒ | Resubmission under MMA? ☐ |
| Collaborative Review Division (*if OTC product*): | | |
| List referenced IND Number(s): 60,663 | | |

| **Goal Dates/Names/Classification Properties** | **YES** | **NO** | **NA** | **Comment** |
|---|---|---|---|---|
| PDUFA and Action Goal dates correct in tracking system?<br><br>***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.*** | yes | | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br>***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.*** | yes | | | |
| Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?<br><br>***If not, ask the document room staff to make the appropriate entries.*** | Yes | | | |
| **Application Integrity Policy** | **YES** | **NO** | **NA** | **Comment** |
| Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*** | | no | | |
| **If yes**, explain in comment column. | | | | |
| **If affected by AIP**, has OC/DMPQ been notified of the submission? **If yes,** date notified: | | | n/a | |
| **User Fees** | **YES** | **NO** | **NA** | **Comment** |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | yes | | | This product was granted an orphan designation and does not need to pay a user fee. |

| | |
|---|---|
| User Fee Status<br><br>***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.*** | Payment for this application:<br><br>☐ Paid<br>☒ Exempt (orphan, government)<br>☐ Waived (e.g., small business, public health)<br>☐ Not required |
| ***If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.*** | Payment of other user fees:<br><br>☒ Not in arrears<br>☐ In arrears |



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***Note:*** *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

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| 505(b)(2)<br>(NDAs/NDA Efficacy Supplements only) | YES | NO | NA | Comment |
|---|---|---|---|---|
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | | no | | |
| Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). | | no | | |
| Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?<br><br>***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).* | | no | | |
| Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***<br><br>**If yes**, please list below: | | no | | |

| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

*If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.*

| Exclusivity | YES | NO | NA | Comment |
|---|---|---|---|---|
| Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** | | No | | |
| **If another product has orphan exclusivity**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?<br><br>***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** | | | na | |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)***<br><br>**If yes**, # years requested: 3<br><br>***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* | yes | | | Firm has also claimed orphan drug exclusivity. |



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| | | | | |
|---|---|---|---|---|
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)? | | no | | |
| **If yes**, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br>***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.*** | | | na | |

| **Format and Content** | | | | |
|---|---|---|---|---|
| ***Do not check mixed submission if the only electronic component is the content of labeling (COL).*** | ☐ All paper (except for COL)<br>☒ All electronic<br>☐ Mixed (paper/electronic)<br><br>☒ CTD<br>☐ Non-CTD<br>☐ Mixed (CTD/non-CTD) | | | |
| **If mixed (paper/electronic) submission**, which parts of the application are submitted in electronic format? | | | | |
| **Overall Format/Content** | **YES** | **NO** | **NA** | **Comment** |
| **If electronic submission,** does it follow the eCTD guidance[1]?<br>**If not,** explain (e.g., waiver granted). | **yes** | | | |
| **Index:** Does the submission contain an accurate comprehensive index? | **yes** | | | |
| Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:<br><br>☐ legible<br>☐ English (or translated into English)<br>☐ pagination<br>☐ navigable hyperlinks (electronic submissions only)<br><br>**If no**, explain. | **yes** | | | |
| **Controlled substance/Product with abuse potential**:<br>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?<br><br>***If yes,*** *date consult sent to the Controlled Substance Staff: 11/28/12* | **yes** | | | |
| **BLAs only**: Companion application received if a shared or divided manufacturing arrangement?<br><br>**If yes**, BLA # | | | **na** | |



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| **Forms and Certifications** | | | | |
|---|---|---|---|---|
| ***Electronic*** *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* | | | | |
| **Application Form** | **YES** | **NO** | **NA** | **Comment** |
| Is form FDA 356h included with authorized signature?<br><br>***If foreign applicant, both the applicant and the U.S. agent must sign the form.*** | yes | | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | yes | | | |
| **Patent Information (NDAs/NDA efficacy supplements only)** | **YES** | **NO** | **NA** | **Comment** |
| Is patent information submitted on form FDA 3542a? | yes | | | |
| **Financial Disclosure** | **YES** | **NO** | **NA** | **Comment** |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?<br><br>***Forms must be signed by the APPLICANT, not an Agent.***<br><br>***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* | yes | | | |
| **Clinical Trials Database** | **YES** | **NO** | **NA** | **Comment** |
| Is form FDA 3674 included with authorized signature? | yes | | | |
| **Debarment Certification** | **YES** | **NO** | **NA** | **Comment** |
| Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)***<br><br>***If foreign applicant, both the applicant and the U.S. Agent must sign the certification.***<br><br>***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* | yes | | | |



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| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
|---|---|---|---|---|
| **For paper submissions only:** Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?<br><br>***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)***<br><br>***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*** | | | na | |

| Pediatrics | YES | NO | NA | Comment |
|---|---|---|---|---|
| **PREA**<br><br>Does the application trigger PREA?<br><br>***If yes, notify PeRC RPM (PeRC meeting is required)***<br><br>***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* | | No | | Orphan indication |
| **If the application triggers PREA**, are the required pediatric assessment studies or a full waiver of pediatric studies included? | | | Na | |
| **If studies or full waiver not included,** is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?<br><br>***If no, request in 74-day letter*** | | | Na | |
| **If a request for full waiver/partial waiver/deferral is included**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)<br><br>***If no, request in 74-day letter*** | | | na | |
| **BPCA (NDAs/NDA efficacy supplements only):**<br><br>Is this submission a complete response to a pediatric Written Request?<br><br>***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)*** | | no | | |



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| Proprietary Name | YES | NO | NA | Comment |
|---|---|---|---|---|
| Is a proposed proprietary name submitted?<br><br>***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.*** | yes | | | |
| **Prescription Labeling** | ☐ **Not applicable** | | | |
| Check all types of labeling submitted. | ☒ Package Insert (PI)<br>☒ Patient Package Insert (PPI)<br>☒ Instructions for Use (IFU)<br>☐ Medication Guide (MedGuide)<br>☒ Carton labels<br>☒ Immediate container labels<br>☐ Diluent<br>☐ Other (specify) | | | |
| | **YES** | **NO** | **NA** | **Comment** |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br>***If no, request in 74-day letter.*** | Yes | | | |
| Is the PI submitted in PLR format? | Yes | | | |
| **If PI not submitted in PLR format**, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request?<br><br>***If no waiver or deferral, request PLR format in 74-day letter.*** | | | na | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC? | Yes | | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) | yes | | | |
| REMS consulted to OSE/DRISK? | Yes | | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA? | yes | | | |
| **OTC Labeling** | ☒ **Not Applicable** | | | |
| Check all types of labeling submitted. | ☐ Outer carton label<br>☐ Immediate container label<br>☐ Blister card<br>☐ Blister backing label<br>☐ Consumer Information Leaflet (CIL)<br>☐ Physician sample<br>☐ Consumer sample<br>☐ Other (specify) | | | |
| | **YES** | **NO** | **NA** | **Comment** |
| Is electronic content of labeling (COL) submitted?<br><br>***If no, request in 74-day letter.*** | yes | | | |



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| | | | | |
|---|---|---|---|---|
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><br>***If no, request in 74-day letter.*** | yes | | | |
| If representative labeling is submitted, are all represented SKUs defined?<br><br>***If no, request in 74-day letter.*** | yes | | | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | yes | | | |
| **Consults** | **YES** | **NO** | **NA** | **Comment** |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) | Yes | | | CSS and CDRH Devices, Human Factors, Compliance, and Tubing |

| **Meeting Minutes/SPAs** | **YES** | **NO** | **NA** | **Comment** |
|---|---|---|---|---|
| End-of Phase 2 meeting(s)?<br>**Date(s):**<br><br>***If yes, distribute minutes before filing meeting*** | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br>**Date(s):** August 7, 2012<br><br>***If yes, distribute minutes before filing meeting*** | yes | | | |
| Any Special Protocol Assessments (SPAs)?<br>**Date(s):**<br><br>***If yes, distribute letter and/or relevant minutes before filing meeting*** | | No | | |

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf



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ATTACHMENT

# MEMO OF FILING MEETING

**DATE**: December 20, 2012

**BLA/NDA/Supp #**: 203952

**PROPRIETARY NAME**: Duopa

**ESTABLISHED/PROPER NAME**: Levodopa Carbidopa Intestinal Gel

**DOSAGE FORM/STRENGTH**: Intestinal Gel

**APPLICANT**: Abbvie Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S)**: Long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease [redacted] (b) (4)

**BACKGROUND**: AbbVie Inc. has resubmitted this New Drug Application (NDA) for Levodopa-Carbidopa Intestinal Gel (LCIG) as a 505(b)(2) after receiving a RTF letter on January 15, 2013. LCIG is a gel formulation of levodopa and carbidopa, delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). LCIG has been developed for the long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease (PD) [redacted] (b) (4)

**REVIEW TEAM**:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|---|---|---|
| Regulatory Project Management | RPM: | Stacy Metz | y |
| | CPMS/TL: | | |
| Cross-Discipline Team Leader (CDTL) | Gerald Podskalny | | y |
| Clinical | Reviewer: | Len Kapcala | y |
| | TL: | Gerald Podskalny | y |
| Biopharmaceutics | Reviewer: | Kelly Kitchens | y |



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| | | | |
|---|---|---|---|
| | TL: | Angelica Dorantes | |
| Pharmacometrics | Reviewer: | Li Zhang | |
| | TL: | Atul Bhattaram | |
| CDRH Devices | Reviewer: | Alan Stevens | |
| | TL: | Jaqueline Ryan | |



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| | | | |
|---|---|---|---|
| Clinical Pharmacology | Reviewer: | Bei Yu | |
| | TL: | Angela Men | |
| Biostatistics | Reviewer: | Xing Lingy | |
| | TL: | Kun Jin | y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Luann Mckinney | y |
| | TL: | Lois Freed | y |
| Statistics (carcinogenicity) | Reviewer: | | |
| | TL: | | |
| CDRH Human Factors | Reviewer: | Quynh Nhu Nguyen | y |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Charles Jewell | y |
| | TL: | Martha Heimann | y |
| CDRH Compliance | Reviewer: | Felicia Brayboy | y |
| | TL: | Carl Fischer | |
| CSS | Reviewer: | Katherine Bonson | y |
| | TL: | Mike Klein | |
| Facility Review/Inspection | Reviewer: | Antoine El Hage | y |
| | TL: | Susan Leibenhaut | n |
| OSE/DMEPA (proprietary name) | Reviewer: | Julie Neshiewat | y |
| | TL: | Irene Chan | |
| OSE/DRISK (REMS) | Reviewer: | Kendra Worthy | y |
| | TL: | Nyedra Booker | y |
| **Patient Labeling** | Reviewer: | Robin Duer | y |
| | TL: | Melissa Hulett | y |

**Labeling—OPDP** **Reviewer:** **Melinda McLawhorn**



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DRAFT



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**FILING MEETING DISCUSSION:**

| | |
|---|---|
| **GENERAL**<br><br>! 505(b)(2) filing issues?<br><br>**If yes,** list issues: | ☐ Not Applicable<br>☐ YES<br>☒ NO |
| ! Per reviewers, are all parts in English or English translation?<br><br>**If no**, explain: | ☒ YES<br>☐ NO |
| ! Electronic Submission comments<br><br>**List comments**: | ☒ Not Applicable |
| **CLINICAL**<br><br>**Comments**: | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| ! Clinical study site(s) inspections(s) needed?<br><br>**If no,** explain: | ☒ YES<br>☐ NO |
| ! Advisory Committee Meeting needed?<br><br>**Comments**:<br><br>***If no, for an original NME or BLA application, include the reason. For example:***<br>o ***this drug/biologic is not the first in its class***<br>o ***the clinical study design was acceptable***<br>o ***the application did not raise significant safety or efficacy issues***<br>o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*** | ☐ YES<br>Date if known:<br>☒ NO<br>☐ To be determined<br><br>Reason: |



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| | |
|---|---|
| ! If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?<br><br>**Comments**: | ☒ Not Applicable<br>☐ YES<br>☐ NO |
| **CLINICAL MICROBIOLOGY**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **CLINICAL PHARMACOLOGY**<br><br>**Comments**: | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| ! Clinical pharmacology study site(s) inspections(s) needed? | ☐ YES<br>☒ NO |
| **BIOSTATISTICS**<br><br>**Comments**: | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)**<br><br>**Comments**: | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **IMMUNOGENICITY (BLAs/BLA efficacy supplements only)**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **PRODUCT QUALITY (CMC)**<br><br>**Comments**: | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |



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| | |
|---|---|
| **Environmental Assessment**<br><br>! Categorical exclusion for environmental assessment (EA) requested?<br><br>**If no**, was a complete EA submitted?<br><br>**If EA submitted**, consulted to EA officer (OPS)?<br><br>**Comments**: | ☒ Not Applicable<br><br>☐ YES<br>☐ NO<br><br>☐ YES<br>☐ NO<br><br>☐ YES<br>☐ NO |
| **Quality Microbiology (for sterile products)**<br><br>! Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)<br><br>**Comments**: | ☒ Not Applicable<br><br>☐ YES<br>☐ NO |
| **Facility Inspection**<br><br>! Establishment(s) ready for inspection?<br><br>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?<br><br>**Comments**: | ☐ Not Applicable<br><br>☒ YES<br>☐ NO<br><br>☐ YES<br>☒ NO |
| **Facility/Microbiology Review (BLAs only)**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **CMC Labeling Review (BLAs/BLA supplements only)**<br><br>**Comments**: | ☒ Review issues for 74-day letter |



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| REGULATORY PROJECT MANAGEMENT | |
|---|---|
| **Signatory Authority:** Billy Dunn, MD<br><br>**21st Century Review Milestones (see attached)** (optional):<br><br>**Comments**: | |
| **REGULATORY CONCLUSIONS/DEFICIENCIES** | |
| ☐ | The application is unsuitable for filing. Explain why: |
| ☒ | The application, on its face, appears to be suitable for filing.<br><br>Review Issues:<br><br>☐ No review issues have been identified for the 74-day letter.<br><br>☒ Review issues have been identified for the 74-day letter. List (optional):<br><br>Review Classification:<br><br>☒ Standard Review<br><br>☐ Priority Review |
| **ACTIONS ITEMS** | |
| ☒ | Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system. |
| ☐ | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| ☐ | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| ☐ | BLA/BLA supplements: If filed, send 60-day filing letter |
| ☐ | If priority review:<br>! notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)<br><br>! notify DMPQ (so facility inspections can be scheduled earlier) |
| ☒ | Send review issues/no review issues by day 74 |
| ☐ | Other |



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## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely



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for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.



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/s/

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STACY M METZ
03/28/2014

# REGULATORY PROJECT MANAGER
# PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
# OF THE PRESCRIBING INFORMATION

**Application:** NDA 203952

**Application Type:** New NDA

**Name of Drug:** Levodopa Carbidopa Intestinal Gel (LCIG)

**Applicant:** AbbVie

**Submission Date: May 28, 2013**

**Receipt Date: May 28, 2013**

## 1.0 Regulatory History and Applicant's Main Proposals

LCIG is a formulation of levodopa and carbidopa delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J).

This NDA provides substantial evidence for the use of LCIG for the following proposed indication: TRADENAME intestinal gel is a combination of levodopa and carbidopa, indicated for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/UCM025576

## 3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 30, 2013. The resubmitted PI will be used for further labeling review.

## 4.0 Appendix



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Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

# Highlights (HL)

## GENERAL FORMAT

**YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

***Comment:***

**NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

***Comment:***

**YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

***Comment:***

**NO** 4. White space must be present before each major heading in HL.

***Comment:***

**YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

***Comment:***



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YES 6. Section headings are presented in the following order in HL:

| Section | Required/Optional |
|---|---|
| ! **Highlights Heading** | Required |
| ! **Highlights Limitation Statement** | Required |
| ! **Product Title** | Required |
| ! **Initial U.S. Approval** | Required |
| ! **Boxed Warning** | Required if a Boxed Warning is in the FPI |
| ! **Recent Major Changes** | Required for only certain changes to PI* |
| ! **Indications and Usage** | Required |
| ! **Dosage and Administration** | Required |
| ! **Dosage Forms and Strengths** | Required |
| ! **Contraindications** | Required (if no contraindications must state "None.") |
| ! **Warnings and Precautions** | Not required by regulation, but should be present |
| ! **Adverse Reactions** | Required |
| ! **Drug Interactions** | Optional |
| ! **Use in Specific Populations** | Optional |
| ! **Patient Counseling Information Statement** | Required |
| ! **Revision Date** | Required |

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

***Comment:***

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

***Comment:***

## HIGHLIGHTS DETAILS

### Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

***Comment:***

### Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

***Comment:***

### Product Title

YES 10. Product title in HL must be **bolded.**

***Comment:***

### Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

***Comment:***

N/A



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# Selected Requirements of Prescribing Information (SRPI)

## Boxed Warning

12. All text must be **bolded**.

    ***Comment:***

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

    ***Comment:***

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

    ***Comment:***

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

    ***Comment:***

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

    ***Comment:***

## Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

    ***Comment:***

N/A 18. Must be listed in the same order in HL as they appear in FPI.

    ***Comment:***

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

    ***Comment:***

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

    ***Comment:***

## Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

    ***Comment:***

## Dosage Forms and Strengths



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NO 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

***Comment:***

**Contraindications**

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

***Comment:***

YES 24. Each contraindication is bulleted when there is more than one contraindication.

***Comment:***

**Adverse Reactions**

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

***Comment:***

**Patient Counseling Information Statement**

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

! **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

! **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**

! **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

***Comment:***

**Revision Date**

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

***Comment:***

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# Contents: Table of Contents (TOC)

**GENERAL FORMAT**

YES 28. A horizontal line must separate TOC from the FPI.

***Comment:***

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".

***Comment:***

YES



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30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

***Comment:***

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

***Comment:***

YES 32. All section headings must be **bolded** and in UPPER CASE.

***Comment:***

YES 33. All subsection headings must be indented, not bolded, and in title case.

***Comment:***

YES 34. When a section or subsection is omitted, the numbering does not change.

***Comment:***

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

***Comment:***

---

# Full Prescribing Information (FPI)

## GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

***Comment:***

YES 37. All section and subsection headings and numbers must be **bolded**.

***Comment:***

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

| |
|---|
| **Boxed Warning** |
| **1 INDICATIONS AND USAGE** |
| **2 DOSAGE AND ADMINISTRATION** |
| **3 DOSAGE FORMS AND STRENGTHS** |
| **4 CONTRAINDICATIONS** |
| **5 WARNINGS AND PRECAUTIONS** |
| **6 ADVERSE REACTIONS** |
| **7 DRUG INTERACTIONS** |
| **8 USE IN SPECIFIC POPULATIONS** |
| **8.1 Pregnancy** |
| **8.2 Labor and Delivery** |
| **8.3 Nursing Mothers** |
| **8.4 Pediatric Use** |
| **8.5 Geriatric Use** |



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| |
|---|
| **9 DRUG ABUSE AND DEPENDENCE** |
| **9.1 Controlled Substance** |
| **9.2 Abuse** |
| **9.3 Dependence** |
| **10 OVERDOSAGE** |
| **11 DESCRIPTION** |
| **12 CLINICAL PHARMACOLOGY** |
| **12.1 Mechanism of Action** |
| **12.2 Pharmacodynamics** |
| **12.3 Pharmacokinetics** |
| **12.4 Microbiology (by guidance)** |
| **12.5 Pharmacogenomics (by guidance)** |
| **13 NONCLINICAL TOXICOLOGY** |
| **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** |
| **13.2 Animal Toxicology and/or Pharmacology** |
| **14 CLINICAL STUDIES** |
| **15 REFERENCES** |
| **16 HOW SUPPLIED/STORAGE AND HANDLING** |
| **17 PATIENT COUNSELING INFORMATION** |

***Comment:***

**YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

***Comment:***

**YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

***Comment:***

**N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

## FULL PRESCRIBING INFORMATION DETAILS

### Boxed Warning

**N/A** 42. All text is **bolded**.

***Comment:***

**N/A** 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

***Comment:***

**N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

***Comment:***

### Contraindications

**N/A** 45. If no Contraindications are known, this section must state "None".



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***Comment:***

**Adverse Reactions**

**YES** 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."*

***Comment:***

**YES** 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."*

***Comment:***

**Patient Counseling Information**

**NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

***Comment:***



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/s/

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STACY M METZ
03/28/2014

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

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| | |
|---|---|
| **DATE:** | February 24, 2014 |
| **TO:** | Charles Jewell, PhD, CMC, Division of Neurology Products, Center for Drug Evaluation and Research, WO-21, Room 2546<br>Stacy.Metz@fda.hhs.gov<br>Office of combination products at combination@fda.gov |
| **Through:** | Cesar Perez, Acting Chief, Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3519<br>Cesar A. Perez -S Digitally signed by Cesar A. Perez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Cesar A. Perez -S, 0.9.2342.19200300.100.1.1=3000413874 Date: 2014.02.24 13:43:17 -05'00' |
| **From:** | Felicia L. Brayboy, Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3547 |
| **Applicant:** | AbbVie Inc.<br>1N Waukegan Road<br>Dept PA77/Bldg AP30<br>North Chicago, IL 60064 |
| **Application #** | NDA 203952 |
| **Product Name:** | Levodopa/Carbidopa Intestinal Gel |
| **Consult Instructions:** | Review of requested additional manufacturing information |

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The Office of Compliance at CDRH received a consult request from CDER regarding Levodopa/Carbidopa Intestinal Gel (LCIG) Administration System, NDA 203952, to review the additional manufacturing information provided in response to our memo dated August 7, 2013.

The Levodopa-Carbidopa Intestinal Gel Administration System is a drug-device combination product that includes the following elements:

- the drug product, Levodopa-Carbidopa Intestinal Gel, 20 mg/mL-5 mg/mL in a medication cassette reservoir; and
- an enteral administration system, known as the LCIG Administration System. This includes: a software-driven, ambulatory infusion pump and a percutaneous endoscopic gastrostomy tube (PEG) with jejunal tube (J), plus an optional, temporary naso-jejunal tube (NJ).

**Application documents evaluation**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following sections of the application were evaluated:

- 3.2.P. Manufacture [3.2.P.7 Container Closure System]
- 1.11. Information Not Covered Under Modules 2 to 5 [ 1.11.1 Quailty Information Amendment and 1.11.4 Multiple Module Information Amendment]
- MAF (b) (4) - pump
- DMF (b) (4) - cassette

The above listed sections of the application contained documents related to Design Controls (820.30), Purchase Controls (820.50), and Corrective And Preventative Actions [(CAPA) 820.100], and other additional information requested.

Design Controls: Standard Operating Procedures (SOPs) or other documentation was provided and addressed all aspects of 21 CFR 820.30. The documentation appeared to be adequate. Below is a list of documents reviewed (this list is not all-inclusive).

Per the firm, the design control process is governed by the following procedures:

- Design Input: Q-11-05-002 Design Input
- Design Output and Design Transfer: Q-11-05-003 Design Output and Transfer
- Design Review: Q-11-05-004 Design Review

- Design Verification: Q-11-05-005 Design Verification
- Design Validation: Q-11-05-006 Design Validation
- Design History File: Q-11-05-010 Managing Design History Files
- Design Changes (completed prior to design transfer): Q-04-05-001 Pre-Transfer Design Change Control
- Design Changes (completed post design transfer): QSD.10.13.01.01 Design Change Impact Assessment
- Risk Assessment Q-11-05-008 Design Risk Management of Combination Products.

Purchase Controls: SOPs or other documentation was provided and addressed 21 CFR 820.50. The documentation appeared to be adequate. Per the firm, purchasing controls are managed using the following documents:

- Overall supplier qualification and control: QSD.18.07.01 Quality Assurance Supplier Evaluation, Monitoring, and Approval
- Supply acceptance activities and conformance to specification: QSD.17.03.01 Material Control/Disposition

Additionally, AbbVie has negotiated Quality Agreements per QSD.18.07.01 Quality Assurance Supplier Evaluation, Monitoring, and Approval for suppliers that will be providing material to the US market. The quality agreements are listed below.

**Quality Agreements**

| Manufacture | Product Provided | Quality Agreement Identifier |
|---|---|---|
| Covidien | Tubing | QTA.Covidien, Tijuana, Mexico *Quality Technical Agreement between Covidien, Tijuana, Mexico and AbbVie* |
| Boston Scientific Corp. | Tubing and Tubing Accessories | QTA.Boston Scientific, Natick, MA *Supplier Quality Technical Agreement for Tubing between Boston Scientific and AbbVie* |
| [redacted] | | (b) (4) |
| Cook Medical, Inc | Tubing and Tubing Accessories | While the tubing is compatible, no QTA is currently available. If a business agreement cannot be reached, labeling will be updated accordingly. |

(b) (4)

| | | |
|---|---|---|
| Smiths Medical | Pump and Pump Accessories | QTA.Smiths Medical<br>*TPM Quality Technical Agreement between Smiths Medical and AbbVie* |

Corrective And Preventative Actions: Standard Operating Procedures SOPs or other documentation was provided and addressed 21 CFR 820.100. The documentation appeared to be adequate. Per the firm, Corrective Action and Preventive Actions are governed by QSD.05.01.01 Investigation Process.

Information regarding the assembly of the finished combination product (drug and delivery system): The pump, drug product, and tubing are not co-packaged in a final presentation or carton by any of the manufacturing facilities or suppliers. Packaging and final acceptance is performed at the manufacturing facilities responsible for each component (e.g., Smiths Medical for the pump, (b) (4) for the filled cassette). As such, the LCIG Administration System consists of independent parts that will be distributed to the health care professional and patient separately and is a combination product through cross-labeling.

The drug product and pump are supplied directly to the clinic/hospital or health care professional prior to initial titration. The health care professional programs the pump according to the patient's response to treatment. Typically, the pump and the initial carton of cassettes would be shipped to the clinic/hospital in the name of the patient. However, there may also be cases where the clinic/hospital or health care professional is unable to receive product in the name of a patient. In those cases, the initial pump and carton would be shipped to the patient's home and patients would bring the unopened shipment to the clinic/hospital.

Tubing sets will be purchased by clinic/hospitals or health care professionals (for

physician placement) via their wholesalers or from AbbVie (AbbVie branded tubing sets). Wholesalers will purchase tubes from appropriate manufacturers, i.e., Covidien, and Boston Scientific. The patient does not receive these materials directly.

After the patient is discharged, they will receive drug product (cartons of seven cassettes each) shipped directly to their home from the AbbVie contracted specialty pharmacy based on the healthcare professional's prescription.

If a patient's pump needs replacement, a new pump will be shipped directly to the patient's home from the LCIG contracted specialty pharmacy. Prior to shipment, the pump is pre-programmed by a health care professional (e.g., pharmacist) specifically for the patient with the appropriate settings.

If a patient needs to have their tubing replaced, this tubing will again be purchased by clinics/hospitals or health care professionals (for physician placement) via their wholesalers or AbbVie prior to the procedure date. The patient does not receive the tubing material directly.

Regulatory history evaluation: Per the Drug Master File (DMF) Smiths Medical ASD, Inc. (St. Paul, MN) is an FDA registered medical device manufacturer through Establishment Registration Number: 2183502. The pump is made here. This site was not listed in the NDA form 356h as a manufacturing site. The last inspection was April 22, 2013 – May 2, 2013 and was classified NAI. This was a medical device inspection. The inspection included coverage of multiple products; a comprehensive QSIT inspection was conducted covering the following systems: Management Controls, Design Controls, CAPA, Production and Process Controls, and Recall Follow-up. No FDA-483, Inspectional Observations was issued, and no verbal observations were made.

[redacted] (b) (4) is a FDA registered medical device manufacturer through Establishment Registration Number [redacted] (b) (4) The cassette is manufactured and assembled at this site. This site was not listed in the NDA form 356h as a manufacturing site. No inspectional history was found for the site. Per the DMF, they comply with 21 CFR 820.30 Design Controls, 21 CFR 820.50 Purchase Controls, and 21 CFR 820.100 Corrective And Preventative Actions (CAPA).

[redacted] (b) (4) is a FDA registered sterile drug manufacturer through Establishment Registration Number [redacted] (b) (4) The cassette is shipped to this site and filled with the drug substance. The last inspection was [redacted] (b) (4) The inspection was classified Voluntary Action Indicated (VAI). This inspection covered the Facilities and Equipment, Laboratory Control, Materials, Packaging and Labeling, Production and Quality Systems.

The previous inspection conducted [redacted] (b) (4) was also classified VAI.

In the memo dated August 7, 2013, CDRH recommended an inspection under the applicable Medical Device Regulations of [redacted] (b) (4) [redacted] The focus of this inspections should be Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100) for the cassette used in the Levodopa/Carbidopa Intestinal Gel Administration System, NDA 203952.

**Deficiencies to be conveyed to the applicant**

There are no deficiencies to be relayed to the applicant.

**CDRH Office of Compliance Recommendation**

The Office of Compliance at CDRH has completed the evaluation of application NDA 203952 and has the following recommendations:

Application NDA 203952 approvability under the Medical Device Regulations should be delayed until the inspection of [redacted] (b) (4) has been completed, the FDA 483 and EIR have been reviewed, and the site is deemed acceptable. The desk review of the application for compliance with the Medical Device Regulations showed no apparent deficiencies.

Felicia L. Brayboy
2014.02.24 11:59:13 -05'00'

Felicia L. Brayboy

Prepared: FBrayboy: February 24, 2014

Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1300209/S001

NDA 203952

**MEMORANDUM**
**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

**Date:** January 6, 2014

**To:** Eric Bastings, M.D., Acting Director
Division of Neurology Products

**Through:** Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

**Subject:** Assessment of abuse potential
Duodopa (NDA 203952); carbidopa and levodopa gel
Indication: Treatment of Parkinson's disease
Sponsor: AbbVie Inc. (formerly Abbott)

This consult finalizes a request by the Division of Neurology Products to evaluate the abuse potential of Duodopa (Levodopa-Carbidopa Intestinal Gel) for the long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease (PD) [redacted] (b) (4) The Sponsor (AbbVie Inc, formerly Abbott Pharmaceuticals) is submitting this drug product as a 505(b)(2) with Sinemet (levodopa/carbidopa) as the reference list drug (RLD). All levodopa/ carbidopa products marketed in the U.S. are unscheduled drugs under the Controlled Substances Act.

CSS acknowledges receipt of the Sponsor's December 13, 2013 email providing the location of information requested by CSS related to abuse potential of the Duodopa.

Based on all information submitted by the Sponsor to date, and in consideration of the lack of abuse-related signals for levodopa/carbidopa in epidemiological data in the medical literature, CSS has concluded that Duodopa does not have abuse potential.

If the Sponsor acquires additional study data or epidemiological reports that show signals of abuse for this drug combination, DNP should consult CSS on this drug product again.

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/s/

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KATHERINE R BONSON
01/06/2014

SILVIA N CALDERON
01/06/2014

MICHAEL KLEIN
01/06/2014

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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# CLINICAL INSPECTION SUMMARY

DATE: December 19, 2013

TO: Stacy Metz, Regulatory Health Project Manager
Leonard Kapcala, M.D. Clinical Reviewer
Division of Neurology Drug Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-952

APPLICANT: AbbVie, Inc.

DRUG: Levodopa Carbidopa Intestinal Gel (Duopa)

NME: No

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Long term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease [redacted] (b) (4)

CONSULTATION REQUEST DATE: September 4, 2013
DIVISION ACTION GOAL DATE: March 28, 2014
INSPECTION SUMMARY GOAL DATE: January 15, 2014
PDUFA DATE: March 28, 2014

## I. BACKGROUND:

The Applicant conducted two identical studies in support of approval for the use of Levodopa-Carbidopa Intestinal Gel (LCIG) in the treatment of patients with Advanced Stages of Parkinson's Disease (PD). Two clinical trials were submitted in support of the application: Protocols S187.3.001 and S187.3.002.

**Protocols:** **S187.3.001and S187.3.002** entitled "A Randomized, Double-Blind, Double-Dummy, Efficacy, Safety and Tolerability Study of Levodopa-Carbidopa Intestinal Gel in Levodopa Responsive Parkinson's Subjects Receiving Optimized Treatments with Parkinson Medical Products who continue to Experience Persistent Motor Fluctuations".

### Investigational Drug

LCIG is suspension of levodopa-carbidopa monohydrate (4:1) (b) (4) The sponsor's claim is that LCIG provides continuous rather than intermittent stimulation of the dopaminergic receptors in the brain by permitting plasma concentration of levodopa to be kept within the individual's therapeutic window.

The delivery of LCIG directly to the proximal small intestine is anticipated to result in the following:

- Continuous delivery of levodopa-carbidopa
- Avoidance of the effects of pulsatile gastric emptying
- Reduced variability in plasma levodopa-carbidopa concentrations
- Decreased motor fluctuations and dyskinesia

LCIG was delivered to the proximal small intestine through a catheter inserted via percutaneous endoscopic gastrostomy (PEG). The LCIG was dispensed in medication cassette reservoirs.

The Applicant stated that LCIG was developed for the long-term treatment of motor fluctuation in patients with advanced (b) (4) Parkinson's disease (PD) (b) (4)

LCIG was intended to address an important unmet medical need in advanced (b) (4) levodopa-responsive PD patients with severe motor fluctuations, (b) (4)

The sponsor sought approval of the new product by submitting data from one pivotal protocol that was combined with data from another study of the same design.

The most common side effects considered drug related include headache, dizziness, nausea, fatigue, drowsiness, device insertion complications, abdominal pain, constipation, orthostatic hypotension, wound infection, erythema, and procedure pain.

**Protocols S187.3.001 and S187.3.002**

These two protocols are identical; therefore, a single description of key design features is presented as follows:

This was a phase 3, 12 week, randomized, double-blind, double-dummy, parallel group, multicenter study of the efficacy, safety and tolerability of LCIG in the treatment of levodopa-responsive subjects with advanced PD and persistent severe motor fluctuations; despite optimized treatment with oral levodopa-carbidopa in addition to other available anti-PFD medications.

Subjects were admitted to the hospital on Study Day 2 to begin the pre-surgical procedures. The PEG-J will be implemented on Study Day 1. The placement target for the jejunal extension is just past the Ligament of Treitz. Following the PEG-J placement, the subjects were randomized to receive either LCIG or to continue oral levodopa-carbidopa IR treatment for 12 weeks. Based on the dummy design, treatment groups wer assigned as follows:

- LCIG + placebo capsules

  or

- Placebo gel + levodopa-carbidopa 100/25 mg IR capsules.

The primary objective of this study was to demonstrate the superiority of treatment with LCIG over treatment with optimized oral levodopa-carbidopa IR during 12 weeks of treatment.

The primary variable was the change from baseline in mean daily "Off" time (hours) based on three consecutive day average of "Off" time for the Parkinson's Disease Diary at Study week 12 (endpoint).

The primary efficacy endpoints in this study were assessed using the Parkinson's Disease Diary, UPDRS, CGI-I, and CGI-S parameters.

Three domestic site inspections were requested in support for this NDA which includes protocols S187.3.001 and S187.3.002

## II. RESULTS (by protocol/site):

| District | Name of CI/Address/ and Site # | Protocol #s and # of Subjects | Inspection Dates | Final Classification |
|---|---|---|---|---|
| Cincinnati | Alberto Espay, M.D.<br>260 Stetson Street, Suite 2300<br>Cincinnati, Oh 4567-0525<br>Site #41279 | Protocol S187-3001/3002<br>9 subjects | 10/28-11/1/2013 | Pending (preliminary classification NAI) |
| Florida | Ramon Rodriguez, M.D.<br>University of Florida Center for Movement Disorder & Neuroretoration<br>2450 Hall Rd, 4th floor<br>Gainsville, Fl 32607<br>Site #41267 | Protocol S187-3001/3002<br>7 subjects | 11/4-6/2013 | Pending (preliminary classification NAI) |
| Cincinnati | John Slevin, M.D<br>Department of Neurology<br>L-443 Kentucky Clinic<br>University of Kentucky Medical Ctr.<br>Lexington, KY 40536-0284<br>Site #9339 | Protocol S187-3001/3002<br>7 subjects | 8/21-27/13 | Pending (preliminary classification NAI) |

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. **Alberto Espay, M.D.**
   **Cincinnati, Ohio, 45267-0525**

   **a. What Was Inspected:** At this site, 10 subjects were screened, one subject was reported as a screen failure, nine subjects were randomized into the study, and all nine subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent forms prior to enrollment.

   The medical records/source documents for all subjects were reviewed. The medical records/source documents for all subjects were reviewed including drug accountability records, vital signs, IRB files, monitoring records, inclusion/exclusion criteria, financial

disclosure, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Espay. Overall, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. However, Subject 107 had adverse events (worsening insomnia, skin irritation, stuffy nose and cold symptoms in study 002. These adverse events continued into the open label for the 003 study and were reported as adverse events for study 003 and inadvertently not submitted for study 002. There were limitations to the inspection.

**c. Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr.Espay's site are considered reliable and acceptable in support of the application.

2. **Ramon Rodriguez, M.D.**
   **Gainsville, FL 32607**

   a. **What Was Inspected:** At this site, a total of 14 were screened, seven subjects were reported as screen failures and the reason(s) were documented. Seven subjects were randomized into the study, and all seven subjects completed the study, were enrolled in the open label Study 003, and continued in Study 005. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

   b. The medical records/source documents for five of the subjects were reviewed. A cursory review of the remaining two subjects was performed and included informed consent, adverse events, concomitant medications, and primary efficacy endpoint. The medical records/source documents for certain subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings.

   c. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Rodriguez. The medical records reviewed were found to be in order, organized, and the data verifiable. Except for minor protocol deviations such as vital signs were not always recorded because three subjects refused due to off time, eating and sleeping. One subject did not sign amendment 6 after a protocol and consent revision from amendment 5 to 6. It is not known what the revisions were. However, the sponsor approved the subject to remain under amendment 5 based on the assessments performed. There were no limitations to the inspection.

   d. **Assessment of Data Integrity:** The data generated at Dr.Rodriguez's site in support of the clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

3. **John Slavin, M.D.**
   **Lexington, KY 40536-0284**

   a. **What Was Inspected:** At this site, a total of 8 subjects were screened, one subject was reported as a screen failure. Seven subjects were randomized into the study, and all completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

   The medical records/source documents for seven subjects were reviewed. The medical records/source documents reviewed included drug accountability records, vital signs, IRB files, monitoring records, sponsor correspondence, inclusion/exclusion criteria, financial disclosure, use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings. There was no evidence of inaccuracy of the data captured. However, the field investigator discussed with the clinical investigator minor discrepancies between the source documents and the data listings. For example, Subject 127-101was documented to have received 400 mg of Sinemet on 3/02/2009 which was corrected to 300 mg on 9/14/1010. This change was not reflected in the data listings. Thus, the impact of the error was minor.

   b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Slevin. The medical records reviewed were found to be in order, organized, and certain data were verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were known limitations to the inspection.

   c. **Assessment of Data Integrity:** The data submitted in support of the clinical efficacy and safety at Dr. Slevin's site are considered reliable and appear acceptable in support of the pending application.

## III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspections of Drs. Espay, Rosriguez, and Slevin revealed no regulatory violations, and the final classifications for these inspections are noted above as No Action Indicated (NAI). The final classification for all sites will be determined upon review of the establishment inspection reports (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.
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CONCURRENCE:

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/s/

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ANTOINE N EL HAGE
12/19/2013

SUSAN D THOMPSON
12/19/2013

KASSA AYALEW
12/19/2013