

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**ADDENDUM TO DEFERRAL OF RISK EVALUATION AND MITIGATION
STRATEGY (REMS) REVIEW**

REMS Review

Date: March 31, 2014

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Reema Mehta, Pharm.D., M.P.H., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Subject: Review evaluates if a REMS is needed for Duopa

Drug Name(s): Duopa® (levodopa/carbidopa) Intestinal Gel

Therapeutic Class: Dopaminergic drug

Dosage form: Intestinal gel (administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using a portable infusion pump)

Application Type/Number: NDA 203-952

Applicant/sponsor: AbbVie, Inc.

OSE RCM #: 2012-2747

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1 INTRODUCTION

This review is an addendum to the Deferral of Risk Evaluation and Mitigation Strategy (REMS) Review, dated February 18, 2014. The review is being amended to document the Division of Risk Management (DRISK) evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Duopa[®] (levodopa-carbidopa intestinal gel), NDA 203-952, received on November 16, 2013 from AbbVie, Inc. (AbbVie). The NDA was submitted to the Division of Neurology Products (DNP) as a 505(b)(2) with Sinemet[®] (levodopa-carbidopa) oral tablets (NDA 017-555) as the reference listed drug.

The Applicant voluntarily submitted a proposed REMS for Duopa on November 16, 2012,

(b) (4)

1.1 PRODUCT BACKGROUND

Duopa, a dopaminergic, is a levodopa-carbidopa intestinal gel (LCIG) that is delivered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using a cassette¹ connected to a portable infusion pump (CADD-Legacy[®] 1400). LCIG is a “therapeutic system” that consists of a drug, device, and insertion procedure. The system is a combination product that contains 20mg/mL levodopa and 5 mg/mL carbidopa monohydrate. Levodopa is the metabolic precursor of dopamine, which is converted to dopamine in the brain. Carbidopa inhibits the peripheral decarboxylation of levodopa, thereby increasing the bioavailability of levodopa in the brain.

The proposed indication is for the treatment of motor fluctuations in patients with advanced Parkinson’s disease (PD). Patients should be levodopa responsive before treatment with LCIG is initiated, and the total daily dose individually titrated to an optimal clinical response for each patient. Dosing is comprised of three components:

1. Morning Dose: (b) (4)
2. Continuous Maintenance Dose: (b) (4) for up to 16 hrs
3. Extra Doses: (b) (4)

The PEG-J is disconnected from the infusion pump at the end of each day, and patients are transitioned to oral levodopa-carbidopa tablets for a post-infusion night-time treatment.

Oral levodopa-carbidopa (LC) tablets should also be administered if there is a need to temporarily discontinue LCIG. Patients should immediately contact their prescriber should this occur.

¹ The cassette used for the Duopa drug product has been custom designed in order to accommodate the drug’s (b) (4) properties.

1.2 DISEASE BACKGROUND

Parkinson's disease (PD) is second to Alzheimer's as the most common neurodegenerative disorder, with an estimated 1 million persons in the United States (5 million worldwide) living with PD.² This progressive and degenerative disease results from a loss of dopaminergic neurons in the substantia nigra. While several environmental, genetic and other physiological factors have been explored, age is the major risk factor for PD with the majority of cases occurring in patients over 50 years of age, but cases can be seen in patients in their 20s, and even younger. In addition, the incidence of PD is 1.5-2 times higher in men.³

Resting tremors, bradykinesia (slow movement), gait impairment (deviation from normal walking pattern) and muscle rigidity are considered "cardinal features" of PD. Additional features can include freezing of gait, postural instability, speech difficulty, autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia, all known as non-dopaminergic features because they do not fully respond to dopaminergic therapy. A PD diagnosis is made based on the presence of these cardinal motor manifestations, and supported by a positive (sustained) response to dopaminergic treatment.

Currently available treatments for Parkinson's Disease for motor symptoms include the following⁴:

- Levodopa/carbidopa oral tablets
- Monoamine oxidase B (MAO B) inhibitors: selegiline
- Dopamine agonists (DAs): bromocriptine, pramipexole, ropinirole, transdermal rotigotine, and apomorphine given by injection
- Catechol-O-methyl transferase (COMT) inhibitors: tolcapone and entacapone
- Anticholinergics: trihexyphenidyl, bentrropine, orphenadrine, procyclidine, and biperiden
- Amantadine

None of the currently available products are approved with a REMS. Levodopa is considered the "gold standard" as the most effective treatment for symptomatic PD however there are limitations to its use, including motor complications which can appear several years after treatment initiation. While the exact cause of levodopa treatment-induced motor complications is unknown, strategies including continuous levodopa infusions have been explored to treat this use-limiting side-effect.

² Olanow CW, Schapira AH. Chapter 372. Parkinson's Disease and Other Movement Disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?aID=9146448>. Accessed December 27, 2013.

³ Xia Y. Chapter 43. Movement Disorders. In: South-Paul JE, Matheny SC, Lewis EL, eds. *CURRENT Diagnosis & Treatment in Family Medicine*. 3rd ed. New York: McGraw-Hill; 2011. <http://www.accessmedicine.com/content.aspx?aID=8156211>. Accessed December 27, 2013.

⁴ Levodopa is often combined with a peripheral decarboxylase inhibitor (e.g., carbidopa) to reduce some of the acute dopaminergic side effects such as nausea, vomiting and orthostatic hypotension that can occur with levodopa therapy.

1.3 REGULATORY HISTORY

August 7, 2012: Type B meeting with Abbott for IND 60-663, in which the Applicant requested Agency comment on a draft risk management plan. The Agency informed the Applicant that it was premature to provide comment and that the Agency would not be in a position to discuss until the review of the submission was underway, and specifically, beyond the mid-cycle point. The Sponsor expressed interest in initiating discussions about the REMS as early as possible in the review cycle.

September 17, 2012: Teleconference with the Applicant and the Human Factors Pre-Market Evaluation Team (HFPMET) to discuss the human factors testing protocol prior to submission of the NDA. The HFPMET supported identifying user tasks required for performance, as ‘essential tasks’ not “safety-critical tasks”.⁵

November 16, 2012: AbbVie submitted a 505(b)(2) NDA for Duopa citing Sinemet as the reference listed drug. The application included a proposed REMS (b) (4)

August 29, 2013: DRISK met with DNP to discuss the Applicant’s proposed REMS. DNP did not anticipate the need for a REMS because the majority of the serious risks with LCIG were recognized risks with PEG-J placement and typically resolved within the first few weeks of treatment. In regards to the proposed ETASU, DNP did not believe that prescriber certification was needed given that the major risks are associated with the procedure, which is performed by a gastroenterologist and not the prescriber (neurologists). DRISK was in concurrence.

September 26, 2013: AbbVie was sent an information request for the following information:

- Rationale for proposing ETASU to mitigate the risks outlined in the proposed REMS
- Provide a process map and written description for the process of dispensing Duopa
- Response regarding whether Duopa will be dispensed directly to both prescribers and patients/caregivers
- Response regarding how Duopa will be dispensed (e.g., mail order distribution)

October 3, 2013: AbbVie provided an email response to the September 26, 2013 information request.

October 7, 2013: REMS Oversight Committee provided concurrence with the team’s proposed strategy that no REMS is necessary for Duopa.

October 30, 2013 (Mid-cycle Meeting): Office of New Drug Quality Assessment (ONDQA) biopharmaceutics reviewer cites concerns with the Applicant’s dissolution test

⁵ The HFPMET agreed with the Sponsor that users (in general) “do not risk catastrophic or serious, permanent injury, but only transient extensions of symptoms already experienced by advanced Parkinson’s patients.”

method's ability to simulate the physiological conditions for administration of Duopa. Additionally, the Center for Devices and Radiological Health (CDRH) identified review issues related to the proposed mechanism for programming the portable infusion pump, and the Division of Medication Error Prevention and Analysis (DMEPA) cited concerns with the proposed instructional documents for patients and healthcare providers.

February 11, 2014: Review team determined that a Complete Response will be issued for NDA 203-952.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

- AbbVie Inc. Response to Agency Information Request, received October 3, 2013
- AbbVie Inc. Proposed REMS for Duopa[®] (Levodopa-Carbidopa) Intestinal Gel, received November 16, 2012

2.2 OTHER MATERIALS INFORMING THE REVIEW

- Clinical Review for NDA 203-952 (L. Kapcala), dated March 13, 2014
- Cross-Discipline Team Leader Review for NDA 203-952 (G. Podskalny), dated March 11, 2014
- Usability Study, Label, and Labeling Review for Duopa (J. Neshiewat), dated February 21, 2014
- REMS Oversight Committee (ROC) - email decision regarding Levodopa-Carbidopa Intestinal Gel, received October 7, 2013
- AbbVie Inc. Draft label for Levodopa-Carbidopa Intestinal Gel, dated August 2013
- AbbVie Inc. Clinical Overview, dated May 28, 2013
- AbbVie Inc. Summary of Clinical Efficacy, dated May 28, 2013
- AbbVie Inc. Summary of Clinical Safety, dated May 28, 2013
- Memorandum of Meeting Minutes. August 7, 2012 Type B Meeting with Abbott, dated September 7, 2012
- Memorandum of Meeting Minutes. September 17, 2012: Teleconference with HFPMET

3 REVIEW FINDINGS FOR DUOPA

3.1 OVERVIEW OF CLINICAL PROGRAM FOR DUOPA

Duopa's safety and effectiveness in the long-term treatment of motor fluctuations in patients with advanced (b) (4) PD was established based on the following clinical studies:

Pivotal Study⁶

Randomized, double-blind, double-dummy, parallel group study

The study was designed to demonstrate the superiority of Duopa over treatment with “optimized” levodopa/carbidopa (LC) oral immediate release capsules, as measured by change from Baseline to Week 12, in “Off” time (*primary endpoint*) and “On” time without troublesome dyskinesia (*secondary endpoint*). A total of 71 advanced PD patients were randomized (37 LCIG/34 LC-oral) to receive the following individually optimized dosing regimens for 12 weeks of treatment:

- Duopa [(20 mg levodopa/5 mg carbidopa per mL) administered via PEG-J and infusion pump] x 16 hrs/day + placebo capsules or
- Placebo gel x 16 hrs/day + LC-oral [(100 mg levodopa/25 mg carbidopa) immediate release (IR) capsules].

Supportive Studies

Long-term, open-label, single-arm, extension study

The study was designed to evaluate long-term safety of Duopa, and assess long-term maintenance of efficacy and health outcome measures. A total of 62 patients completing the pivotal study were enrolled in the extension study and received the following individually optimized dosing regimen for 12 months of treatment:

- Duopa [(20 mg levodopa/5 mg carbidopa per mL) administered via PEG-J and infusion pump] x 16 hrs/day.

Long-term, open-label study

The study was designed to evaluate long-term safety and tolerability of Duopa in advanced, levodopa-responsive PD patients with severe motor fluctuations despite optimized treatment with available anti-PD medications, and to assess long-term maintenance of efficacy and health outcome measures. A total of 354 advanced PD patients received the following individually optimized dosing regimen:

- Duopa (20 mg levodopa/5 mg carbidopa per mL) x 16 hrs/day; administered as an initial 2-14 day nasojejunal (NJ) infusion test period, followed by a 12 month treatment period via PEG-J and infusion pump.

3.1.1 Efficacy⁷

The primary endpoint (change from Baseline to Week 12 in normalized “Off” time) and key secondary endpoint (change in “On” time without troublesome dyskinesia) were assessed based on data recorded by patients in a Parkinson’s Disease Diary⁸. Additional secondary endpoints were primarily assessed using the following tools: Parkinson’s

⁶ The original US Clinical Development Program for LCIG included two, Phase 3 pivotal studies of identical design that recruited study subjects from distinct study sites. These identical studies were combined (prior to database lock) as one pivotal study.

⁷ AbbVie, Inc. Summary of Clinical Efficacy (dated May 28, 2013).

⁸ Parkinson’s Disease Diary is a validated tool to capture patient-defined assessment of clinical status on various motor symptoms including “Off” time and “On” time.

Disease Questionnaire (PDQ-39)⁹, Unified Parkinson's Disease Rating Scale (UPDRS)¹⁰, and the Clinical Global Impression-Improvement (CGI-I)¹¹.

Statistical significance was achieved in the pivotal trial for both the primary and key secondary endpoint. There was a significantly greater decrease in "Off" time [mean difference (improvement) of -1.91 hours in favor of Duopa;(p=0.0015)]¹², and significantly greater increase in "On" time without troublesome dyskinesia [mean difference (improvement) of 1.86 hours in favor of Duopa;(p=0.0059)]¹³, in patients after 12 weeks of treatment with Duopa (at individually optimized dosing) compared to LC-oral (100 mg/25 mg IR capsules).

Significant improvement was also observed in patients treated with Duopa (vs. LC-oral) for the following additional secondary endpoint measures: improvement in PD symptoms [measured by PDQ-39; mean difference of -7.0 with a decreasing score representing improvement in PD symptoms; p=0.0155], improvement in clinical status [measured by CGI-I; mean difference of -0.7 with a lower score indicating greater improvement in clinical status; p=0.0258] and improvement in PD-associated activities of daily living [measured by UPDRS Part III; mean difference of -3.0 with a decreasing score representing improvement in PD symptoms; p=0.0086].

Statistical significance was not achieved on measures of motor impairment (UPDRS Part II; p=0.5020), health status (EuroQol Quality of Life 5 Dimensions¹⁴; p=0.0670) and level of burden for caregivers (Zarit Burden Interview¹⁵; p=0.1501).

3.1.2 Safety¹⁶

Safety was evaluated based on events likely related to the Duopa therapeutic system (levodopa-carbidopa combination drug product, device, and PEG-J procedure required to facilitate drug delivery). Non-procedure and device-associated treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients (and at a greater rate with Duopa vs. LC-oral) in the Phase 3 pivotal study were nausea (18.9% vs 14.7%), constipation (13.5% vs. 5.9%), and flatulence (13.5% vs. 11.8%).

⁹ Parkinson's Disease Questionnaire (PDQ-39) is a validated patient-reported rating scale to assess the clinical status of motor symptoms (e.g., "on/off" time) over a period of time.

¹⁰ Unified Parkinson's Disease Rating Scale (UPDRS) is a clinician-administered, 5-part tool that follows the "longitudinal course" of a PD patient and captures measure such as behavior, mood, activities of daily living and complications of therapy.

¹¹ Clinical Global Impression-Improvement (CGI-I) is performed by the investigator and measures change in clinical status after treatment.

¹² Least squares (LS) mean change: reduction in "off time" of 4.04 hours for LCIG group and 2.14 hours for LC-oral group (LS mean difference (improvement) of 1.91 hours).

¹³ Least squares (LS) mean change: increase in "on time" of 4.11 hours for LCIG group and 2.24 hours for LC-oral group (LS mean difference (improvement) of 1.86 hours).

¹⁴ EuroQol Quality of Life-5 Dimensions (EQ-5D) is a patient-reported outcome measure of quality-of-life

¹⁵ Zarit Burden Interview (ZBI) is a caregiver-reported outcome measure.

¹⁶ AbbVie, Inc. Clinical Overview and Summary of Clinical Safety (dated May 28, 2013).

The incidence of treatment-emergent serious adverse events (TESAEs) was less with Duopa (14%) than with LC-oral (21%). The most common TESAEs ($\geq 2\%$) observed during the open-label treatment period (*in descending order*) included: complication of device insertion, pneumonia, abdominal pain, peritonitis, Parkinson's disease, hip fracture, polyneuropathy, weight decreased, pneumoperitoneum, device dislocation, postoperative wound infection, fall, and pneumonia aspiration. The clinical review did not identify a clear dose-dependent relationship for developing a TESAE among the 3 dose levels categorized.¹⁷

There was only 1 patient who discontinued Duopa following a TEAE in the active-controlled trial. The patient reported hallucinations and psychosis, which are labeled events for LC-oral, while receiving "Low dose LCIG".

Seventeen deaths were reported, with all occurring in the open-label trials during long-term treatment with Duopa. One death (cardiac arrest) was considered as *possibly* related to treatment. Two deaths were labeled "completed suicides"; both patients had histories of depression.

DNP Clinical Reviewer Comment¹⁸: *The number of patients who died and the adverse events associated with the death did not raise unusual concerns. Considering that this is a relatively older population of patients with advanced Parkinson's disease and many other associated diseases/disorders, this fatality rate and causes of fatality seemed reasonable for the population and the total duration of patient treatment and monitoring.*

[Regarding the 2 completed suicides]: *It is not possible to conclude that there is an increased risk for suicidality or completed suicide with LCIG [Duopa] treatment. However, LCIG [Duopa] does appear to increase the risk for depression. It is possible that additional insight into the risk for suicide could be obtained by conducting a 6 month controlled trial in the postmarketing period and monitoring patients for the risk for suicidality and depression at baseline and throughout 6 months treatment. I recommend that we make a Postmarketing Requirement for such a trial.*

3.1.3 Human Factors Studies

The Sponsor proposed the following patient and healthcare provider-focused materials to support safe and efficacious use of the Duopa therapeutic system:

- Patient Instructions for Use

 (b) (4)

¹⁷ Dose levels: Low dose Duopa (<1250 mg/day), High dose Duopa (≥ 1250 -2000mg/day, ≥ 2000 mg/day, "Any High Dose") and Any Dose.

¹⁸ Clinical Review for NDA 203952-Levodopa/Carbidopa Intestinal Gel (L. Kapcala), dated March 13, 2014.

¹⁹ The Sponsor combined the " (b) (4)" per Agency request. The combined IFU contains additional warnings and precautions not previously captured in the patient labeling used in the human factors study. DMEPA does not believe that these changes warrant another human factors simulated use study.

- Healthcare Provider Instructions for Use

(b) (4)

Human factors studies were conducted with 50 participants [25 patients and 25 healthcare providers (nurses and neurologists)] performing *essential tasks* associated with the use of Duopa in “intended use environments” to include the home and other non-clinical locations, as well as the clinical environment for initial device set-up and routine maintenance. Study participants were not assessed on performance of PEG-J insertion, NJ tube insertion, long-term PEG-J care or stoma care.

Task failures and operational difficulties were analyzed to inform risk mitigation strategies. No situations were identified by the Sponsor that placed study subjects at risk for death or serious permanent injury. The Sponsor concluded that the most frequently identified user errors had minimal impact on user safety.

The Center for Devices and Radiological Health (CDRH) and Division of Medication Error Prevention and Analysis (DMEPA) reviewed the Human Factors studies under a separate review. CDRH outlined several deficiencies, including gaps in testing and warning statements. DMEPA recommended labeling changes to the instructions for use (IFU) and a labeling comprehension study.²⁰

3.2 SAFETY CONCERNS

3.2.1 Safety Profile for Oral Levodopa-Carbidopa

Combination oral levodopa-carbidopa is considered the primary standard and mainstay treatment for PD patients. Despite its effectiveness, patients with advanced PD receiving LC-oral often experience motor symptoms at the end of each dose (wearing-off) or levodopa-induced dyskinesia, given fluctuations in the plasma levels of orally administered levodopa due to its short half-life and variability in gastric emptying. Patients taking LC-oral should be monitored for the development of depression and suicidal tendencies, thought to be due to increased dopamine levels in the brain following levodopa administration. In addition, LC-oral should be administered with caution in patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease. Patients with a history of peptic ulcers should be monitored closely while receiving LC-oral products, as treatment with levodopa may increase the risk for upper gastrointestinal hemorrhage.

Cases of a complex resembling Neuroleptic Malignant Syndrome (NMS) have been reported in patients experiencing an abrupt dose reduction or discontinuation of LC-oral therapy. Patients undergoing these dose adjustments should be observed closely.

Patients on dopaminergic drugs including levodopa, may be at an increased risk for somnolence or in rare cases, episodes of sudden sleep onset without awareness or warning (sleep attack). Approved labeling for SINEMET® (carbidopa-levodopa) states

²⁰ Usability Study, Label, and Labeling Review for NDA 203952-Duopa (Carbidopa and Levodopa) Enteral Suspension (J. Neshiewat), dated February 21, 2014.

that patients must be informed of this risk and advised to exercise caution while driving or operating machines.²¹

Parkinson's patients are at greater risk for melanoma as compared to the general population. While it remains unclear as to whether there is a link to drugs used to treat PD, the SINEMET® labeling recommends periodic skin examinations for patients.

Impulse control disorders have been documented in PD patients and believed to be associated with the use of dopamine agonists. The potential drug-associated increased risk for urges (e.g., sexual urges or urges to gamble) is described under PRECAUTIONS in the approved label for oral carbidopa-levodopa.

3.2.2 Safety Profile for Duopa

While the potential benefits of Duopa over LC-oral include more consistent dopaminergic levels to the brain of PD patients upon intestinal infusion, resulting in an improvement in clinical symptoms, serious safety concerns with this formulation have been identified.

The clinical reviewer (L. Kapcala) identified the following as "Submission Specific Primary Safety Concerns" with Duopa:

Procedure/Device-Associated Events

Serious procedure- and device-associated adverse events of special interests (AESIs) were reported in 13.9% (55/395) subjects over 590.2 patient-years (mean exposure 546 days). The most common AESIs reported in $\geq 1\%$ of subjects are summarized below:

- **Titration Period (Days 1-28):** Serious procedure- and device-associated AESIs were reported in 8.1% (32/395) subjects during the 28-day Titration Period. Events included complication of device insertion (4.8%), peritonitis (2.5%), abdominal pain (2.3%), and pneumoperitoneum (2.3%).
- **Maintenance Period (Day 29 up to Day 1276):** Serious procedure- and device-associated AESIs were reported in 7.9% (30/382) subjects during the long-term Maintenance Period. Events included complication of device insertion (2.9%), abdominal pain (1.6%), post-operative wound infection (1.0%), device occlusion (1.0%), and small intestinal obstruction (1.0%).

The aforementioned events are consistent with safety issues associated with the use of PEG or PEG-J tubes for other indications.

The adverse events associated with the LC component of the device were consistent with the safety profile for the oral formulation (as described in Section 3.2.1.). In addition to the risks associated with the class of LC products, the following safety issues were reviewed:

²¹ SINEMET® (carbidopa-levodopa) approved product labeling.

Polyneuropathy

The Sponsor convened an adjudication committee of 3 neurologists with expertise in peripheral neuropathy to review cases reported during the Duopa clinical development program. The committee identified 19 cases that met the criteria for generalized polyneuropathy. Most cases were mild in severity and the majority believed to be associated with vitamin deficiency. The adjudication committee concluded that the risk of peripheral neuropathy is greater in Duopa exposed patients than would be expected in a comparable population (including a comparable PD population treated with oral levodopa). Additionally, patients with pre-existing neuropathy or diseases that increase susceptibility to the condition (e.g., diabetes) would be at greater risk for developing LCIG-induced neuropathy.

According to the DNP clinical reviewer, there were no cases of polyneuropathy in the controlled trial. Many cases of TEAEs categorized as polyneuropathy were however, reported in the pooled, open-label trials. The incidence of polyneuropathy was 12% (24 patients) in the 4 Month Safety Update, with all cases developing during the maintenance period.

Clinical Reviewer Comment²²: I believe that it is possible that the risk of polyneuropathy associated with LCIG treatment may be related to oral LD itself, hydrazine, associated vitamin deficiencies (e.g., B12, B6, folic acid) and a possible combination of these factors. If this product is approved, it may be desirable to monitor vitamin levels before and periodically after treatment and include these recommendations in the label.

3.3 RISK MANAGEMENT PROPOSED BY APPLICANT

AbbVie proposed a REMS with elements to assure safe use (ETASU) (b) (4)

AbbVie's proposed REMS for Duopa includes the following elements: (b) (4)

The proposed REMS includes the following goals and elements: (b) (4)

²² L. Kapcala (Clinical Review).

4 DISCUSSION

Advanced PD patients can experience persistent motor fluctuations despite optimized oral levodopa-carbidopa therapy. These patients often alternate between periods of good motor-system control without troublesome dyskinesia, and unpredictable shifts to periods of slowness, stiffness and poor mobility (“On-Off” phenomenon). In this population of patients, after oral therapy becomes insufficient at addressing motor fluctuations, the only available non-pharmacologic treatment option is deep brain stimulation (DBS). While DBS can provide significant improvement in motor fluctuations and overall quality of life, severe and irreversible side effects can occur due to the surgical procedure (e.g., intracerebral bleeding, stroke), device (e.g., wires breaking, infection) and stimulation process (e.g., oculomotor disturbances, dysarthria).

Duopa is a “therapeutic system” consisting of the levodopa-carbidopa combination drug product, device and insertion procedure. The drug is administered into the jejunum via percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using a portable infusion pump. If approved, Duopa would represent the only therapy that provides continuous levodopa administration via intestinal infusion.

The efficacy of Duopa over LC-oral for the long-term treatment of motor fluctuations in patients with advanced Parkinson’s Disease were demonstrated in the pivotal study, and include the following:

- Statistically significant improvement (reduction) in the average daily “Off” time (1.91 hours), as measured by data recorded by patients in a Parkinson’s Disease Diary.
- Statistically significant improvement (increase) in the average daily “On” time (1.86 hours), as measured by data recorded by patients in a Parkinson’s Disease Diary.

Most of the risks observed with Duopa (e.g., dyskinesia, somnolence, and impulsive/compulsive behavior) in the clinical development program are consistent with the recognized risks associated with LC-oral.

GI and GI-procedure related risks

There are however, several GI and GI-procedure related risks associated with the Duopa therapeutic system including intestinal obstruction, postoperative wound infection, pneumoperitoneum, device occlusion and peritonitis. To mitigate these GI and GI-procedure related risks, the Sponsor proposed a REMS with ETASU (see Section 3.3) and proposed inclusion of risk information in the Warnings and Precautions and Adverse Reactions sections of the prescribing information.

Most serious GI and GI procedure-related events observed with the Duopa therapeutic system were considered to be recognized risks associated with the use of PEG or PEG-J tubes for other indications. Many of these adverse events resolved within the first 4 weeks of treatment, and no deaths were reported in the active controlled study. In regards to the proposed REMS ETASU, prescriber certification is not needed given the major risks are associated with the procedure, which is performed by gastroenterologists and

not prescribers (neurologists). There does not appear to be anything unique about the risks associated with the placement of PEG-J in the Duopa therapeutic system. Therefore, DRISK and DNP concur that a REMS is not required to address GI adverse events associated with the use of Duopa and labeling would be sufficient. The team presented the recommendation to the REMS Oversight Committee and received agreement.²³

Polyneuropathy

Most cases of polyneuropathy reported in the pooled, open-label trials were mild in severity and the majority believed to be associated with vitamin deficiency and occurred during the maintenance period. Based on the available data, patients with pre-existing neuropathy or diseases that increase susceptibility to the condition (e.g., diabetes) would be at greater risk for developing LCIG-induced neuropathy. Therefore, DNP recommends the prescribing information include a Warning and Precaution regarding the risk of polyneuropathy and a recommendation to monitor vitamin levels.

DRISK believes that labeling will be sufficient to address the aforementioned risks; therefore, additional risk mitigation strategies are not warranted.

Human Factors Studies

Human factors studies tested patients and healthcare provider's abilities to perform essential tasks associated with the use of Duopa. No situations were identified by the Sponsor that placed study subjects at risk for death or serious permanent injury. The Sponsor concluded that the most frequently identified user errors had minimal impact on user safety. Reviewers from DNP, CDRH, and DMEPA did not identify safety concerns that would warrant a REMS. Therefore, information in the prescribing information and instructions for use are sufficient to mitigate any safety issues associated with improper use of the device.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Duopa (levodopa-carbidopa) intestinal gel. Duopa has proven efficacy in the treatment of PD. The serious risks of concern associated with the administration of Duopa are procedure and device associated risks (e.g., intestinal obstruction, wound infection, polyneuropathy, pancreatitis), polyneuropathy, and known adverse events associated with LC. The procedure-related risks are recognized risks associated with the use of PEG-J for other indications. Thus, the benefit-risk profile for Duopa is favorable and the risks can be mitigated through professional labeling.

Should DNP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

²³ The DRISK and DNP recommendation that a REMS is not required to address adverse events associated with Duopa was presented to the REMS Oversight Committee (ROC) on September 13, 2013, and the ROC concurred.

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/s/

NYEDRA W BOOKER
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Deferral of Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 18, 2014

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

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Drug Name(s): Levodopa-Carbidopa Intestinal Gel (proposed trade name-Duopa)

Therapeutic Class: Dopaminergic drug

Dosage and Route: 20 mg levodopa/1mL and 5 mg carbidopa monohydrate/1 mL in cassettes containing approximately 100 grams of gel; administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using a portable infusion pump

Indication(s): Treatment of Parkinson's disease-associated motor fluctuations

Application Type/Number: NDA 203-952

Applicant/sponsor: AbbVie, Inc.

OSE RCM #: 2012-2747

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This document is to defer comment on AbbVie, Inc.'s proposed Risk Evaluation and Mitigation Strategy (REMS) for Duopa (levodopa-carbidopa intestinal gel), voluntarily submitted with NDA 203-952 to the Division of Neurology Products (DNP) on November 16, 2012. The NDA was submitted as a 505(b)(2) with Sinemet® (levodopa-carbidopa) oral tablets (NDA 017-555) as the reference listed drug.

1.1 BACKGROUND

Duopa, a dopaminergic, is a levodopa-carbidopa intestinal gel (LCIG) that is delivered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using a cassette¹ connected to a CADD-Legacy 1400 portable infusion pump. The proposed indication is for the treatment of motor fluctuations in patients with advanced Parkinson's disease (PD). Patients should be levodopa responsive before treatment with LCIG is initiated, and the total daily dose individually titrated to an optimal clinical response for each patient. Dosing is comprised of three components:

1. Morning Dose: (b) (4)
2. Continuous Maintenance Dose: (b) (4) for up to 16 hrs
3. Extra Doses: (b) (4)

The PEG-J is disconnected from the infusion pump at the end of each day, and patients are transitioned to oral levodopa-carbidopa tablets for a post-infusion night-time treatment.

Oral levodopa-carbidopa tablets should also be administered if there is a need to temporarily discontinue LCIG. Patients should immediately contact their prescriber should this occur.

2 RISK MANAGEMENT PROPOSED BY APPLICANT

AbbVie's proposed REMS for LCIG includes the following elements: (b) (4)

The proposed REMS includes the following goals and elements:

(b) (4)

¹ The cassette used for the Duopa drug product has been custom designed in order to accommodate the drug's viscous properties.

3 DISCUSSION

At the October 30, 2013 Mid-cycle meeting, the Office of New Drug Quality Assessment (ONDQA) biopharmaceutics reviewer sited concerns with the Applicant's dissolution test method's ability to simulate the physiological conditions for administration of LCIG.

Additionally, the Center for Devices and Radiological Health (CDRH) identified review issues related to the proposed mechanism for programming the portable infusion pump, and the Division of Medication Error Prevention and Analysis (DMEPA) sited concerns with the proposed instructional documents for patients and healthcare providers.

On February 11, 2014, the review team met to discuss Agency concerns and possible options for moving forward. DNP subsequently determined that a Complete Response will be issued for NDA 203-952 by the March 28, 2014 Action Date; therefore DRISK defers comment on the Applicant's REMS proposal at this time.

A final discussion of the REMS will be undertaken after the Applicant resubmits the application for review. This memo serves to close the existing request for DRISK review of AbbVie, Inc.'s proposed REMS for Duopa (levodopa-carbidopa intestinal gel) under NDA 203-952.

Please notify DRISK if you have any questions.

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/s/

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02/18/2014

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