CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203952Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	203952
Applicant Name	AbbVie Inc.
Date of Submission	7/11/14
PDUFA Goal Date	1/11/15
Proprietary Name/ **Established (USAN) Name**	Duopa/levodopa-carbidopa
Dosage Forms/Strength	Enteral suspension: 20 mg/mL levodopa-4.63 mg/mL carbidopa
Proposed Indication(s)	Treatment of motor fluctuations in patients with advanced Parkinson's disease
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Leonard Kapcala, MD
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC/OBP Review	Charles Jewell, PhD; Kelly Kitchens, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
OPDP	N/A
OSI	N/A
CDTL Review	Dave Podskalny, DO
OSE/DMEPA	Jacqueline Sheppard, PharmD
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	N/A
PMHS	N/A
SEALD	N/A
Other	Alan Stevens (CDRH Engineering); QuynhNhu Nguyen (CDRH Human Factors)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Abbvie originally submitted in May 2013 a 505(b)(2) New Drug Application (NDA) to support the marketing of levodopa carbidopa enteral suspension (LC) for the treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (PD). On March 28, 2014, based upon manufacturing, device performance, and human factors deficiencies in the initial application, the Division issued a Complete Response (CR) letter for that application.

The current submission is a complete response to the CR letter. It consists primarily of new and additional chemistry, engineering, and human factors data, discussion, and analyses intended to address the previously identified deficiencies.

As the application was reviewed in detail during the first cycle, I will briefly discuss the applicant's resubmission and the major findings of the members of the review team who reviewed the resubmission. I refer to my summary review of 3/28/14 along with the various first cycle reviews of the members of the review team for a discussion of the initial application and the issues leading to the CR action.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

In the first review cycle, FDA identified the following deficiencies that formed the basis of the CR action:

- "…deficiencies related to product quality that require additional information for validation of your revised control methods, additional dissolution profile information, and additional stability data."

- "…additional information concerning the specification, software, and potential hazards for the CADD-Legacy Model 1400 pump."

- "…deficiencies in your human factors assessment that require modification and reassessment."

It is also important to note that the CR letter did not cite deficiencies concerning effectiveness or safety (other than safety as it relates to the above CR deficiencies). Substantial evidence of effectiveness was provided in the initial application and there were no safety concerns that precluded approval.

3. CMC/Device

The applicant has provided additional information addressing the product quality issues identified in the CR letter. This information has been carefully reviewed by Dr. Jewell and Dr. Kitchens and summarized by Dr. Podskalny. All agree that the applicant has adequately addressed the deficiencies identified in the initial application. I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of no more than 24 months when stored frozen (-20°C) and no more than 12 weeks when stored at refrigerated temperature (2°C to 8°C). When warmed to room temperature it should be used the same day or discarded. There are no outstanding issues.

The applicant has provided additional information addressing the device issues related to software function and hazards testing identified in the CR letter. This information has been carefully reviewed by the device engineering reviewer, Mr. Stevens, and summarized by Dr. Podskalny. Both agree that the applicant has adequately addressed the deficiencies identified in the initial application. I concur with their conclusions. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The applicant has provided additional information addressing the human factors issues identified in the CR letter. The applicant implemented modifications to the Instructions for Use and assessed the impact of these modifications in a new summative human factors study that included 9 healthcare providers and 6 patients. This information has been carefully reviewed by the human factors reviewers, Dr. Sheppard and Ms. Nguyen, and summarized by Dr. Podskalny. All agree that the modifications to the Instructions for Use have improved the ability of users to use the product, that risks have been mitigated to an acceptable level, and that the results of the new human factors study support safe and effective use by the intended

users. I concur with their conclusions. There are no outstanding human factors issues precluding approval.

8. Safety

The sponsor included a safety update in the resubmission, as required. This was reviewed in detail by Dr. Kapcala. He concludes that the additional information in the safety update does not change the safety profile characterized in his initial review and notes that no new clinically important or unexpected safety findings were observed. Dr. Podskalny summarized the additional information and agrees. I concur that there are no new or outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A (orphan designation)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The applicant has provided additional information that acceptably addresses the manufacturing, device performance, and human factors deficiencies that formed the basis of the original CR action. As noted above, substantial evidence of effectiveness was provided in the initial application and there are no safety concerns in either the initial application or the resubmission that preclude approval. There are no outstanding unresolved issues.

There are no necessary postmarketing requirements or commitments.

Specific postmarketing risk management activities are not needed.

We have agreed with the applicant on product labeling that describes the effectiveness and safety of levodopa carbidopa enteral suspension (20 mg/mL levodopa-4.63 mg/mL carbidopa) for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

For these reasons, I will issue an approval letter for this NDA, to include the agreed-upon product labeling.

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

/s/

WILLIAM H Dunn
01/09/2015

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	203952
Applicant Name	AbbVie Inc.
Date of Submission	5/28/13
PDUFA Goal Date	3/28/14
Proprietary Name / **Established (USAN) Name**	Duopa/levodopa-carbidopa
Dosage Forms / Strength	Intestinal gel: 20 mg/mL levodopa-5 mg/mL carbidopa
Proposed Indication(s)	Long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Leonard Kapcala, MD
Statistical Review	Xiang Ling, PhD
Pharmacology Toxicology Review	LuAnn McKinney, DVM
CMC Review/OBP Review	Charles Jewell, PhD; Kelly Kitchens, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Bei Yu, PhD
OPDP	Melinda McLawhorn, PharmD, BCPS
OSI	Antoine El-Hage, PhD
CDTL Review	John Marler, MD
OSE/DMEPA	Julie Neshiewat, PharmD; Liu Liu, PharmD
OSE/DDRE	N/A
OSE/DRISK	Nyedra Booker, PharmD
OMP/DMPP	Robin Duer, MBA, BSN, RN
PMHS	N/A
SEALD	N/A
Other	Alan Stevens (CDRH Engineering); QuynhNhu Nguyen (CDRH Human Factors), Katherine Bonson, PhD (CSS)

OND=Office of New Drugs
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OSE=Office of Surveillance and Epidemiology
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DDRE=Division of Drug Risk Evaluation
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OMP=Office of Medical Policy
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SEALD=Study Endpoints and Labeling Development

1. Introduction

Sinemet (levodopa-carbidopa (LC)) in both standard and sustained release preparations of various strengths is an approved drug product for the treatment of Parkinson's disease.

AbbVie Inc. (Abbvie) has submitted a 505(b)(2) application for the approval of levodopa carbidopa intestinal gel (LCIG) efficacy supplement for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (PD) (b) (4) Sinemet is the reference listed drug for this application. LCIG is a combination product consisting of drug (LC), pump, and associated tubing for direct intestinal infusion through a jejunal (J) tube via a standard percutaneous endoscopic gastrostomy (PEG) tube.

In addition to the established safety and effectiveness of Sinemet, the application relies on the usual array of supportive data and the results of a primary clinical trial evaluating efficacy, supportive observational safety studies, and a clinical pharmacokinetic study.

The overall recommendation of the review team is against approval. The CDTL, Dr. Podskalny, has provided a detailed summary of the findings of the review team, and agrees with this recommendation. This recommendation is based on chemistry and manufacturing issues along with device issues related to engineering and usage. The primary clinical data supporting this application have been found acceptable by the review team. I will discuss the major findings leading to the recommendation against approval and will briefly discuss the other aspects of the application.

2. Background

Sinemet was initially approved in 1975 and a sustained release preparation was approved in 1991. It is one of the primary treatments for PD with extensive clinical use. Its efficacy and safety are well characterized. The approved label for Sinemet indicates that dosing should be individualized and describes a maximum recommended dose of 2000 mg of levodopa and 200 mg of carbidopa. The label states that experience above these levels is limited. Despite the use of Sinemet and other approved drugs for the treatment of PD, over time, patients with advanced PD experience disabling motor fluctuations from the "on" state to the "off" state based upon varying levodopa concentrations. Eventually, these become persistent and are resistant to any further changes in drug regimen. Continuous administration of levodopa is thought to lead to greater stability in concentrations and thus fewer motor fluctuations in this difficult to treat group of patients. This is the basis for LCIG.

LCIG has orphan drug designation. LCIG has been approved in 41 other countries, beginning in 2004, and is marketed in 25 of those countries. While two primary clinical studies supporting approval were planned, they were combined into a single study due to difficulty with recruitment. The Division agreed to this approach at a Type C meeting in 2011.

3. CMC/Device

Dr. Podskalny has summarized the findings of Dr. Jewell, the CMC reviewer. There are concerns with [redacted] and dissolution that argue against approval.

[redacted] of the drug product was observed during annual stability testing of the approved foreign product. A series of maneuvers to control this were attempted by the sponsor, but [redacted] continued to be observed. [redacted] The applicant has hypothesized [redacted] ill resolve the [redacted] issue, but has not yet submitted the data. As Dr. Jewell notes, "Although the logic and preliminary data of this change has been discussed with the agency, we are awaiting the confirmatory data to support this finding. Homogeneity needs to be maintained for up to 24 months of frozen storage, followed by up to [redacted] weeks of refrigerated storage, and up to 24 hours at room temperature to support the proposed use of the product."

The applicant did not submit acceptable dissolution information with the initial application. Although the applicant attempted to justify this omission, discussions with the applicant indicated that an acceptable assessment of dissolution was required. Although several amendments to the application contained additional dissolution information, the data were insufficient to support approval as they did not include complete multipoint dissolution profile data and were not tested under appropriate conditions.

Manufacturing site inspections were acceptable.

The engineering review of the infusion pump identified several issues related to software function and hazards testing that preclude approval. They are summarized in Dr. Podskalny's review and include questions regarding pump accuracy, adequacy of software documentation, and an extensive list of device hazards that affect the rate of infusion.

Human factors reviews were conducted by Ms. Nguyen (CDRH) and Dr. Neshiewat (DMEPA) and summarized by Dr. Podskalny. Both Ms. Nguyen and Dr. Neshiewat identified deficiencies in the human factors evaluation of the combination product. Deficiencies include inconsistencies in the Instructions for Use contained in the initial application and the [redacted] for the infusion pump submitted as an amendment to the application, and the presence of warnings and cautions in an updated Instructions for Use that were not assessed in representative patients in the human factors study. In addition, there were multiple task failures associated with the correct use of the infusion pump that could lead to incorrect dosing and adverse patient outcomes. Ms. Nguyen concluded that an additional human factors study was necessary to demonstrate that the product could by used by patients and health care provides safely and effectively. Dr. Neshiewat concluded that improvements in labeling should be made, including revisions to the Instructions for Use and the combination of two infusion pump instructions manuals, followed by a comprehension study to assess these

changes in labeling and instructions. Dr. Podskalny has considered the clinical impact of the task failures seen in the original human factors study and concludes that an additional human factors study is warranted.

4. Nonclinical Pharmacology/Toxicology

As discussed by Dr. Podskalny, the nonclinical reviewer, Dr. McKinney, finds concerns with the presence of three degradants (hydrazine, (b) (4), and (b) (4)) that exceed acceptable levels at the proposed shelf-life limits.

The sponsor justifies the levels of hydrazine, a known animal carcinogen, with a discussion of nonclinical literature, a comparison to hydrazine exposure in patients treated with isoniazid, a comparison of hydrazine exposure in patients treated with LCIG and standard oral LC, and the lack of carcinogenic risk in patients treated with approved LCIG outside the US.

The sponsor justifies levels of (b) (4) and (b) (4) with a 4-week rat toxicity study, in vitro genotoxicity assays, and animal and human pharmacokinetic data, and argues that both are metabolites of carbidopa in humans.

Dr. McKinney, Dr. Lois Freed, and Dr. Podskalny all have extensive discussions in their reviews of these data and the issues surrounding these three impurities, and I will not repeat those here. Dr. McKinney concludes that (b) (4), as a metabolite of carbidopa, is not of concern; that (b) (4) has not been qualified because the 4-week rate study is too short (3 months is needed for chronic therapies); and that the levels of hydrazine exceed the allowable daily exposure and are not acceptable. Dr. Freed, when considering Dr. McKinney's conclusions, argues that some reassurance can be taken from the 4-week rat study for both (b) (4) and (b) (4) and that the experience with marketed LCIG combined with the inability of the sponsor to further reduce the levels of these two impurities suggests that a 3-month study is not needed for approval, despite the lack of full qualification for either one. Dr. Freed agrees that hydrazine has not been qualified. While Dr. McKinney feels the levels of hydrazine and (b) (4) preclude approval, Dr. Freed, in her supervisory memo, argues that, given the severity of the intended patient population, if the clinical benefit warrants approval, the presence of these degradants does not necessarily preclude approval, and, post-approval, the sponsor may be asked to explore strategies for reducing the amounts of these degradants under conditions of storage and use. Dr. Podskalny concurs with this approach.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Notably, consistent levodopa levels were maintained over the course of infusion and there was lower pharmacokinetic variability of levodopa after LCIG dosing when compared to standard oral LC, consistent with the intent of the LCIG formulation.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Podskalny, Dr. Kapcala, and Dr. Ling, data supporting efficacy is the product of two primary clinical trials that were combined into a single trial due to difficulty with recruitment. The Division agreed to this approach at a Type C meeting in 2011. This was a randomized, double-blind, double-dummy, multicenter, parallel-group trial of LCIG compared with standard oral LC in the treatment of levodopa-responsive subjects with advanced PD who had persistent motor fluctuations, despite optimized treatment with oral levodopa-carbidopa and other available antiparkinsonian medications as adjunctive treatment. Dosing was flexible and was adjusted in response to perceived benefit and side effects. A discussion of the dosing approach is on pages 51-55 of Dr. Kapcala's review and an analysis of doses administered is on pages 82-87. As Dr. Kapcala points out, in general, the doses of LCIG used (along with total levodopa) are largely within the range of those used with conventional oral LC. Per his review, the mean daily levodopa dose for LCIG patients was slightly less than 1200 mg and the mean daily levodopa dose for oral LC was about 1400 mg, with the overwhelming majority of patient receiving less than 2000 mg of levodopa. There were 35 LCIG patients and 31 LC patients who completed the study. As described by Dr. Ling, the primary efficacy endpoint was the change from baseline in the average daily normalized "off" time based on the 3 consecutive day average normalized "off" time for the symptom diary at Week 12. "Off" time was normalized to a 16-hour waking time to account for variation in the subjects' sleep time and was calculated as (Absolute "off" time/Awake time)*16. The key secondary efficacy endpoint was the change from baseline in normalized "on" time without troublesome dyskinesia (normalized "on" time without dyskinesia or with non-troublesome dyskinesia) based on the 3 consecutive day average normalized "on" time without troublesome dyskinesia for the symptom diary at week 12. A detailed discussion of these findings is presented by the clinical reviewers and is summarized below.

	change in hours of "off" time, baseline to week 12, LS means
LC	-2.14
LCIG	-4.04
difference	-1.91 in favor of LCIG
p-value	0.0015

	change in hours of quality "on" time, baseline to week 12, LS means
LC	2.24
LCIG	4.11
difference	1.86 in favor of LCIG
p-value	0.0059

Various sensitivity analyses of these outcomes were consistent and supportive.

8. Safety

The safety profile of the currently approved formulation of LC is well established and described in labeling. Dr. Kapcala and Dr. Podskalny present a thorough discussion of safety analyses related to the current submission. Safety was assessed both in the trial supporting efficacy and in three long-term open-label supportive safety studies. Several issues warrant specific mention.

There were no deaths in the controlled trial, though there were 18 deaths in the open-label cohort (n=412), none of which appear to raise specific concern about LCIG.

Serious adverse events associated with the use of LCIG appear similar in character to those experienced with LC in trials in patients with advanced PD.

There were no adverse events associated with PEG and J tube placement that appeared out of the ordinary for those procedures.

There was a small numerical excess (4 patients) of depression in the controlled trial for LCIG along with depression and two suicides in the open-label studies. Current labeling for LC includes a warning regarding this issue.

Neuropathy has been reported in post-marketing surveillance of LCIG outside the US. While no cases occurred in the short-term controlled trial, there were reports of neuropathy in the open-label observational studies that appeared consistent with the post-marketing reports. Their relationship to LCIG is uncertain and Dr. Podskalny points out that there have been reports of neuropathy with standard LC.

There are no clear signs of toxicity associated with hydrazine. Dr. Kapcala found that the rate of malignancy seen in the open-label studies was comparable to age-adjusted background rates.

Overall, Dr. Kapcala and Dr. Podskalny feel that there are no safety findings that preclude approval.

The sponsor proposed a REMS (with ETASU) in the application. Dr. Booker defers detailed comment on the proposed REMS due to the other deficiencies in the application, and Dr. Podskalny notes that the REMS Oversight Committee agreed with the Division's recommendation that a REMS was not needed for this application.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A (orphan designation)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been deferred pending resolution of the outstanding deficiencies.

13. Decision/Action/Risk Benefit Assessment

I agree with the members of the review team that this application should not be approved due to deficiencies associated with the performance of the device component of the combination product, the manufacturing process of the drug component, and the need for further human factors evaluations. The review team has been in frequent contact with the sponsor in an attempt to resolve these various deficiencies during the review cycle, but, after careful consideration, it is apparent that they are not resolvable during the current cycle.

The applicant has provided substantial evidence of effectiveness from the combination of two identical trials analyzed and submitted for review as a single trial, as supported by the known benefits and effects of approved Sinemet, for the use of LCIG as a treatment for advanced PD.

The presence of high levels of hydrazine is of potential concern. Dr. Podskalny argues that patients with advanced PD have limited treatment options at this stage in the disease and may be contemplating invasive neurosurgical treatments in an attempt to gain relief from the severely debilitating nature of their symptoms. With appropriate surveillance, he feels that the potential increased risk of carcinogenicity is acceptable for this population and does not preclude approval. I agree. There are no other safety concerns that preclude approval, and the long-term experience with approved Sinemet will serve to inform the substantial portion of the safety profile of LCIG. I agree that a REMS is not needed.

Consideration of postmarketing requirements will be deferred to the next review cycle.

Because of the manufacturing, device performance, and human factors deficiencies identified in the application, I will issue a complete response letter for this NDA.

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

/s/

WILLIAM H Dunn
03/28/2014