

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203952Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203952

SUPPL #

HFD # 120

Trade Name Duopa

Generic Name Carbidopa and Levodopa Enteral Suspension

Applicant Name AbbVie Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17555 Sinemet 19856 Sinemet CR

NDA# 21485 Stalevo 17830 Lodosyn

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

S187-3-001 and S187-3-002

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 S187-3-001

YES NO

Investigation #2 S187-3-002

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 S187-3-001

YES NO

Investigation #2 S187-3-002

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

S187-3-001 and S187-3-002

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 S187-3-001

IND # 60663 YES ! NO
! Explain:

Investigation #2 S187-3-002

IND # 60663 YES ! NO
! Explain:

APPEARS THIS WAY ON ORIGINAL

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

/s/

STACY M METZ
12/29/2014

WILLIAM H Dunn
12/29/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203952 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: DUOPA Established/Proper Name: carbidopa/levodopa Dosage Form: enteral suspension		Applicant: AbbVie Agent for Applicant (if applicable):
RPM: Tracy Peters/Stacy Metz		Division: Division of Neurology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: 1/8/15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>January 11, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Complete Response 3/28/14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain: <u>N/A</u>		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
1. List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
2. Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
3. Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Complete Response 3/28/14 Approval 1/9/15
Labeling	
4. Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
5. Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use (patient and prescriber) <input checked="" type="checkbox"/> Device Labeling (see both IFUs and PI) <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
6. Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
7. Proprietary Name	Review 10/28/14 Letter 10/30/14
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	
8. Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 10/3/14 DMEPA: <input type="checkbox"/> None 12/12/14 and 1/6/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 12/10/14 OPDP: <input type="checkbox"/> None 12/8/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input type="checkbox"/> None 1/6/14 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
9. RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	
10. All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 3/5/14
11. NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
12. Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> 	
13. Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	RTF Letter 1/15/13
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
14. Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 8/7/12
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Type A 3/14/13 Type A 6/10/14
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
15. Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/9/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/11/14 and 12/22 14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
16. Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review see CDTL Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	3/13/14 and 12/24/14
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review 3/13/14
Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

17. Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 1/6/14
18. Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	5/28/13 Submission included a REMS. ROC Committee and DRISK determined a REMS was not needed and the sponsor was informed in their CR letter. See emails and DRISK review. <input type="checkbox"/> None
19. OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 12/19/13
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
20. Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/21/14
Clinical Pharmacology <input type="checkbox"/> None	
21. Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/28/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
22. Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 3/8/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/21/14
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
23. Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceuticals reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/9/14 and 1/28/14 Biopharm 2/21/14 and 12/1/14
24. Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 8/1/13
25. Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None CDRH/Device 2/27/14 and 12/18/14 CDRH/Human Factors 3/6/14 and 10/17/14 CDRH Compliance 2/24/14
26. Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC Review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
27. Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 3/7/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested (see action letter) <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

STACY M METZ
01/22/2015

From: Metz, Stacy
To: [Kuntz, Matthew \(matthew.kuntz@abbvie.com\)](mailto:matthew.kuntz@abbvie.com)
Subject: DMEPA Comments, Med Guide, and IFUs
Date: Tuesday, December 16, 2014 3:38:00 PM
Attachments: [Duopa FINAL MEDICATION GUIDE 12 16 14.docx](#)
[Duopa FINAL Patient IFU 12 16 14.docx](#)
[DUOPA FINAL prescriberIFU 12 16 14.docx](#)
Importance: High

Hi Matt,

I am emailing to provide you the DMEPA Comments, a combined DMEPA/ONDQA Comment, Med Guide and both IFUs.

Please see the following recommendations from DMEPA:

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 [REDACTED] (b) (4) as the dosing calculation provided in Section 2 are provided in volume (e.g., 100 ml [REDACTED] (b) (4)). This will allow for uniformity between the prescribing information and the label.
4. Ensure the proprietary name, established name, and strength are the most prominent information on the Principal Display Panel.

B. Container Label

1. Increase the prominence of the storage requirements by using either bolded letters or larger font size. This will alert dispensing pharmacy pharmacies and patients to the unique storage requirements of the product.
2. Add a statement similar to “Use product at room temperature” to mitigate the risk of missed dose related to pump failure due to clogged product.
3. Express the net quantity as volume [REDACTED] (b) (4) as the dosing information provided in Section 2 is provided in volume, as is the statement of strength (expressed per

mL). This will allow for consistency between the prescribing information and the label.

4. Ensure the proprietary name, established name, and strength are the most prominent information on the Principal Display Panel.

(b) (4)

Additional DNP/ONDQA Combined Comment:

Currently marketed oral solutions comprised of more than one active ingredient present the strength as a single

statement separated by slashes. We request that Duopa be presented as 4.63 mg/20 mg per mL. This will need to be reflected on all components of your label/labeling. Please update all documents when you respond to us.

Please let me know if you have any questions. I will be in touch as soon as I have a final ok on the PI.

Best Regards,

Stacy

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

/s/

STACY M METZ
12/18/2014



NDA 203952

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AbbVie Inc.
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

ATTENTION: Matthew Kuntz, PharmD, MBA, RAC
Director, Regulatory Affairs

Dear Dr. Kuntz:

Please refer to your New Drug Application (NDA) dated and received November 16, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Carbidopa and Levodopa Enteral Suspension, 4.63 mg/20 mg per mL.

We also refer to your correspondence, dated and received August 22, 2014, requesting review of your proposed proprietary name, Duopa.

We have completed our review of the proposed proprietary name, Duopa and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your August 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Tracy Peters, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2953.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
10/30/2014



NDA 203952

MEETING MINUTES

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

Dear Dr. Kuntz:

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

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2014. The purpose of the meeting was to discuss the issues in the March 28, 2014, Complete Response Letter and to gain the Agency's agreement on AbbVie's plan for a Complete Response Resubmission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: June 10, 2014, 11:00-12:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: NDA 203952
Product Name: Levodopa Carbidopa Intestinal Gel (LCIG)
Indication: Parkinson's disease
Sponsor/Applicant Name: AbbVie

Meeting Chair: Billy Dunn, MD
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES

Billy Dunn, MD, Acting Director
Gerald David Podskalny, DO, Clinical Team Leader
Leonard Kapcala, MD, Clinical Reviewer
Martha Heimann, PhD, CMC Lead, ONDQA
Charles Jewell, PhD, Chemistry Reviewer, ONDQA
Kellie Taylor, PharmD, MPH, Acting Director, DMEPA
Tingting Gao, PharmD, DMEPA Acting Team Leader
Jacqueline Sheppard, PharmD, DMEPA Reviewer
Charlene Flowers, OSE (DPVI)
Quynh Nhu Nguyen, MS, CDRH Combination Products Human Factors Specialist
Alan Stevens, CDRH Pump Reviewer
Jeffrey Cooper, DVM, CDRH Tubing Branch Chief
Branden Reid, PhD, CDRH Tubing Reviewer
Patricia Love, MD, MBA, Office of Combination Products
Bindi Nikhar, MD, Office of Combination Products
Stacy Metz, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Andrew Storey, BSc, Vice President, US and Canada Regulatory Affairs
Donna Helms, BS, MBA, RAC, Director, Global Regulatory Affairs
Ed Israelski, PhD, Director, Human Factors
James Duhig, PhD, Manager, CMC Device Regulatory Affairs (Human Factors)

James Erker, MS, Director, Quality Assurance, Combination Products and Medical Devices
Janet Benesh, BSMT, Project Director, Neuroscience Development – R&D
Jordan Dubow, MD, Medical Director, Neuroscience Development – R&D
Katherine Wortley, PhD, RAC, Associate Director, CMC Device Regulatory Affairs
Matthew Kuntz, PharmD, RPh, MBA, RAC, Director, US and Canada Regulatory Affairs
Douglas Feltner, MD, Vice President, Neuroscience Development
Terrance Ocheltree, PhD, Sr. Director, Regulatory CMC

1.0 BACKGROUND

AbbVie submitted a 505(b)(2) application for levodopa-carbidopa intestinal gel (LCIG) on November 16, 2012. A Refusal to File (RTF) letter was received on January 15, 2013. AbbVie resubmitted the New Drug Application (NDA) on May 28, 2013. On March 28, 2014, the Food and Drug Administration (FDA) issued a Complete Response Letter (CRL). AbbVie requested a joint face-to-face Type A End of Review and Center for Devices and Radiological Health (CDRH) Submission Issue meeting with the Agency for the purpose of discussing the issues in the March 28, 2014, Complete Response Letter and gaining the Agency's agreement on AbbVie's plan for a Complete Response Resubmission.

The purpose of the meeting is to:

- Discuss AbbVie's plan to respond to the issues and requests for additional information within the CRL.
- Obtain agreement on the human factors risk analysis for this patient population.
- Gain consensus on the acceptability of the supplemental human factors study.
- Concurrence on Smiths Medical and AbbVie's conclusions regarding the pump issues noted within the CRL.
- Agree on the timing and mechanism for AbbVie to submit the 15-week stability data.
- Discuss coordination of the associated enteral tubing device premarket notification (510[k]) submissions

The meeting request, including meeting package, was submitted on April 11, 2014.

2.0 DISCUSSION

2.1. CDRH Human Factors

Question 1:

Advanced PD patients may experience symptoms of poor mobility, dyskinesia, suboptimal therapy, and discomfort on a daily basis despite treatment with their current anti-PD medications. These are the same potential health outcomes which may be experienced sporadically by patients who may have occasional difficulty using the LCIG system. Because these potential outcomes do not represent a new risk, AbbVie would like to gain concurrence from the FDA (all disciplines reviewing the application, i.e., CDRH/HFPMET, CDER/DMEPA and DNP) that anticipated residual risks such as noted in the previous human factors study are acceptable. Does the Agency agree?

FDA Response to Question 1:

The perceived residual risks may change as a result of additional modifications made to the pump operation, Instructions for Use, and additional Human Factors testing results. For clarity, please provide an updated list of items you consider to be a residual risk in your resubmission. At this time, we consider the acceptability of residual risks to be a review issue.

Meeting Discussion:

The Sponsor stated were no changes made to the pump or its operation and they believe the residual risks presented in the original NDA are unchanged by the results of the recent Human Factors Testing. FDA stated that the information presented to the Agency in the original NDA and at this meeting suggest that the residual risk is acceptable and unchanged from the NDA. However, the Agency needs to review the recently completed Human Factors Testing results to conclude the residual risks are unchanged by this new information.

Question 2a:

AbbVie requests Agency comment on the following aspects of the proposed supplemental human factors study.

- a. AbbVie intends to test only critical tasks (as previously defined) in the supplemental human factors study (Appendix B). Since the non-critical steps were evaluated in the previous human factors study they will not be scored and evaluated in the supplemental human factors study. Does the Agency agree?

FDA Response to Question 2a:

Yes, we agree. Please see our comments regarding critical tasks under FDA response to question 2c (specifically comments # 1, 3, and 4 below).

Meeting Discussion:

No further discussion at the meeting.

Question 2b:

Per FDA request, the supplemental human factors study will include 15 total participants, approximately half patients and half HCPs (nurses and pharmacists). Neurologists will not be included as they have limited interactions with the pump and are usually assisted by trained nurses. Does the Agency agree?

FDA Response to Question 2b:

No, we do not agree with the human factors (HF) study protocol, as described. We recognize that we previously requested a minimum of 15 participants. In our review of the currently proposed labeling and protocol, we note that some changes to labeling have been made since we issued the Complete Response (CR) letter, and your protocol is testing some tasks that were not evaluated in your previous HF studies. We note the following changes that were not included in your previous HF studies or have been made since the time of the CR:

- Alarms: Only low battery and high pressure alarms were tested in the previous human factors validation study. Other alarms were not tested and may elicit different responses by users.
- Health care provider (HCP) user programming tasks associated with Lock Level 1 were not evaluated as part of the previous HF studies.
- Your combined Instructions For Use (IFU) were not included in your previous human factors testing. The patient combined IFU, which contains warnings and precautions statements that were not included in your previous HF testing, was reviewed by the Agency prior to the CR but was not validated in your previous HF Study. The HCP combined IFU was neither reviewed by the Agency nor validated in your previous HF studies.

Because the changes may affect the way the users understand and interact with the device, these changes could impact the safe and effective delivery of drug. As a result, these changes should be validated. The users impacted include HCPs and patients; therefore, your study should include a minimum of 15 users in each of these groups for a total of 30 participants: HCPs (n=15) and patients (n=15).^{1,2} We agree that you need not include neurologists as they are expected to have limited interactions with the pump.

Meeting Discussion:

Although FDA previously requested a minimum of 15 participants from each unique user group to validate the changes made to the device and the IFU, AbbVie explained that no changes were made to the user tasks or to the hardware or software of the device. AbbVie further clarified that changes made to the IFUs for both patients and the health care providers were intended to help the users complete the tasks successfully. FDA provided suggestions for AbbVie to provide a

¹ Applying Human Factors and Usability Engineering to Optimize Medical Device Design, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf>

² Faulkner, L. (2003). Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. *Behavior Research Methods, Instruments, and Computers*, 35(3), 379-383.

standalone study report for the supplemental validation study and a new integrated summary of the validation results from all human studies conducted in the resubmission to facilitate FDA review. Additionally, FDA recommended a summative study report with a table showing each critical task and the participant performance across studies so that FDA may review the validation data collectively.

Question 2c:

Does the Agency have any further comments or suggestions on the enclosed supplemental human factors study protocol?

FDA Response to Question 2c:

Please see comments below:

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 does not clearly describe the mitigations you plan to implement and it did not focus on demonstrating their effectiveness. To complete our review, please provide:
 - a. 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 specific errors and operational difficulties that were observed in the previous HF study that each modification is designed to address,
 - b. An explanation of how your protocol design focuses on evaluating those specific changes to provide data that can confirm the changes are effective at reducing use errors and do not introduce any new hazards.
2. Your protocol did not include follow-up interview questions for any use errors or failures that users may experience during simulated use testing. We consider these subjective assessments to be essential and HF Usability and Validation testing, and they are incomplete without them. Please modify your protocol to include direct discussion using open-ended questions for all use errors and failures of critical tasks for each test participant. Note that you should define failures as actions or incidents of failure to act that may potentially or would inevitably cause a negative clinical impact.
3. Regarding your proposal to only test a sample of the alarms, warning and caution statements, it is possible that the sample may not include critical alarms, warnings, and caution statements and if a user fails to respond properly, it could lead to patient harm. Please ensure that critical alarms, warnings, caution statements, and their associated tasks are included in the study. Test all alarms, warnings, and caution statements identified in your risk assessment as being critical to the correct use of this product. Any remaining alarms, warning and caution statements can be prioritized for further testing. Please provide your rationale for the prioritization.

4. Because some alarms, warning and caution statements represent critical tasks for users (e.g., detecting, understanding, and taking action/inaction), include an assessment of these tasks in an abbreviated analysis of use-related risk and assess user performance of these tasks in in your supplemental HF study. Your analysis should include potential use errors and associated harm (negative clinical consequences) of each task and (as per deficiency #1 above) the risk-mitigation strategies you have applied. You may submit this response by appending 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 an assessment of the 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 described 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.
7. In your protocol, you state there will be no time limit for completion of any task and participants may use all available resources but in the event that the participant becomes too physically fatigued to complete the test, testing may be continued in another session. If testing continues in another session, designate the task as incomplete and analyze the results separately.
8. We recommend that your patient sample include an adequate number of patients that qualify to test the user tasks associated with Lock Level 1 (LL1). Ensure that approximately half of your patient group completes user tasks for LL1. Your study results should specify the number of patients assigned to user tasks associated with each lock level.
9. Training for this study should mimic the anticipated training in clinical practice with a single training session followed by a minimum 24-hour training decay period.
10. For the assessment of pump programming by Health Care Providers, ensure that approximately half are assigned to program LL1 and half to program LL2.

Meeting Discussion:

FDA asked Abbvie to ensure that the response to the CR Letter addresses all of the CR deficiencies. Also, the new/supplemental study report should include a summary table that links all of the HF studies, and discusses task performance and implemented mitigations. Each study report can be referenced and included as an Appendix to the summary table.

FDA asked about the number of participants enrolled to test each lock level. AbbVie explained that all LL2 tasks are included in LL1 tasks, and that participants must perform LL2 tasks in order to perform LL1 tasks. AbbVie further explained that 25 patients and 25 HCPs were tested

on LL2 tests in the original Human Factors study. AbbVie also completed a supplemental validation study to include 15 patients on completing LL1 tasks and 10 HCPs on setting the lock level for patient use. FDA suggested AbbVie to provide a summary table of the validation results from all human factors studies conducted in the resubmission to allow efficient FDA review.

FDA agrees with AbbVie's explanation that a single training session does not mimic clinical practice and that multiple training sessions are required due to the patient's advanced Parkinson's disease and the complexity of this combination product. FDA asked whether the IFU was used during training and AbbVie explained that the IFU was used in addition to other support materials and demonstrated a "Welcome Kit" that included a pre-loaded video board for the end users.

FDA further asked whether patients' ability to wait 20 minutes after removing the cassette from the refrigerator was tested and explained in the patient IFU. AbbVie confirmed that it tested patients' comprehension but did not make participants physically wait 20 minutes. Additionally, AbbVie clarified that information regarding the rationale of the waiting period was concisely explained in the IFU and well understood during testing. FDA also asked if AbbVie made any changes to the instructions on the morning dose double button press. AbbVie confirmed that it did make revisions in the IFU regarding the formatting of the instructions for the button presses and participants were able to successfully complete the morning dose steps in the validation study.

2.2. CDRH Devices (Pump)

Question 3:

The data within the MAF supports the Dose Volume accuracy specification and represents the conditions a patient may experience. Does the Agency concur that this list of studies (Table 3) and associated data in the MAF adequately addresses CDRH Request 1b?

FDA Response to Question 3:

The response is acceptable.

Meeting Discussion:

No further discussion at the meeting.

Question 4:

Does the Agency concur that the test method proposal will address CDRH Request 1d?

FDA Response to Question 4:

You have proposed to evaluate the 0.1 mL/hour delivery rate over a (b) (4) period. We recommend that the test period be changed to model the 16-hour daily infusion period.

Meeting Discussion:

No further discussion at the meeting.

2.2. Product Quality

Question 5:

Does the Agency agree with the proposed post-approval stability commitment?

FDA Response to Question 5:

This commitment is reasonable but the final decision on agreement is pending the review of the data presented in the complete response package. It is possible that we will require morning dose testing on stability for the post approval commitment, but we will consider your request ^(b)₍₄₎ pending review of the complete data set.

Meeting Discussion:

No further discussion at the meeting.

Question 6:

Does the Agency agree with AbbVie's plan to submit the 8-week stability data with the Complete Response Resubmission and to submit the full 15-week stability data within 2 months of the resubmission?

FDA Response to Question 6:

This is acceptable.

Meeting Discussion:

No further discussion at the meeting.

2.3. Safety Update

Question 7:

Does FDA agree with AbbVie's plan for the post-action safety update?

FDA Response to Question 7:

Yes, we agree.

Meeting Discussion:

No further discussion at the meeting.

2.4. CDRH Tubing

AbbVie has submitted three 510(k) Premarket Notification submissions to CDRH (K133087, K133096, and K133129) for enteral tubing products that are labeled specifically for use with Duopa. These 3 submissions are pending responses to questions communicated to AbbVie on November 22, 2013. AbbVie would like to revisit the timing for clearance of the 510(k)s.

AbbVie recognizes that the Agency has indicated that drug approval and device clearance would be coordinated and that AbbVie may need to withdraw and resubmit the device submissions to align with drug approval timing. In order to minimize CDRH review resources, AbbVie proposes to submit the responses to CDRH in advance of the 180 day due date which is May 21, 2014 to enable completion of the current review. AbbVie requests the Agency complete the current ongoing review cycle through product clearance and allow AbbVie to control release to the field pending NDA approval.

Question 8:

Does the Agency agree with this proposal?

FDA Response to Question 8:

Please see combined comment below for Question 8 and 9.

Question 9:

If the above request is not acceptable, are there other options that would minimize CDRH review resources?

FDA Response to Question 9:

Please see combined comment below for Question 8 and 9.

FDA Response to Questions 8 and 9:

The Gastroenterology Devices Branch (ODE / FDA) received the Supplements to your 510(k) applications (K133087, K133096, and K133129). You have removed (b) (4)

and revised your IFU Statements with administration of medication instead. Generally, PEG tubes, J tubes, and NJ tubes, include the administration of medication within the IFU Statement; therefore, your new IFU Statements are acceptable. (b) (4)

Meeting Discussion:

No further discussion at the meeting.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

For any revised document providing instruction for Duopa use, the Agency requested that the revisions in the document be presented from several perspectives:

- 1) as a tracked changes version showing every change (i.e., any addition or any deletion) regardless of how complicated the document may appear;*
- 2) as a 3 column table showing the previous version of information, the revised language, and a summary of the rationale for each revision;*
- 3) as a detailed narrative description of all revisions; and*
- 4) as a clean version.*

6.0 ATTACHMENTS AND HANDOUTS

The sponsor provided a table prior to the meeting in response to our preliminary responses (attached).

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

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
07/09/2014

Metz, Stacy

From: Booker, Nyedra
Sent: Friday, February 21, 2014 3:29 PM
To: Podskalny, Gerald
Cc: Metz, Stacy; Mehta, Reema
Subject: RE: REMS review for NDA 203952 LCIG

Hi Gerald,

In response to your email below, yes DRISK still agrees with the decision that a REMS is not required for LCIG.

Thanks,

Nyedra

From: Podskalny, Gerald
Sent: Thursday, February 20, 2014 3:36 PM
To: Booker, Nyedra
Cc: Metz, Stacy
Subject: REMS review for NDA 203952 LCIG

Hi Nyedra,

I read your review which is a defers of the REMS review for this product. Although the applicant will receive a CR action letter, the Division will have to put REMS language in the CR letter or leave that portion of the letter blank (our intention). The sponsor will interpret this as meaning that a REMS is not required for this product and a REMS will not be included in the resubmission. I know we have agreement from the ROC that a REMS is not necessary for LCIG but I just want to be sure DRISK agrees with the decision that a REMS is not required for Levodopa Carbidopa Intestinal Gel. Thanks.

Dave

Gerald David Podskalny, D.O., M.P.H.S.
Cross Disciplinary Team Leader
Division of Neurology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Bldg 22, Room 4377
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone 301-796-2778 (DNP 796-2250)
DNP Fax 301-796-9842
Email gerald.podskalny@fda.hhs.gov

Metz, Stacy

From: Metz, Stacy
Sent: Thursday, December 12, 2013 12:08 PM
To: Yasuda, Sally
Cc: Ngan, Kelly
Subject: Duopa (levodopa carbidopa) NDA 203952 REMS Decision

Hi Sally,

Please see email string below.

When this NDA came in (5/28/13) the sponsor included a REMS with ETASU. Alice and Kelly were invited to the meetings at the beginning and Alice attended the first couple when the REMS was discussed, along with Kendra Biddick and DRISK. The team decided that a REMS was not needed for this product and everyone was in agreement. Also, the ROC committee met and also agreed with us that a REMS was not needed.

We had not informed the sponsor yet and they called questioning any REMS discussion. From there, please see Dave's email below that we can let the sponsor know. We just wanted to run this past you to see if there is anything specific we need to tell them or anything we need to follow (since Alice is out).

Thanks! Let me know if you need more information. I am including the link in case you want to take a look.

EDR Location: <\\CDSESUB1\EVSPROD\NDA203952\203952.enx>

Stacy

From: Podskalny, Gerald
Sent: Wednesday, December 11, 2013 2:33 PM
To: Metz, Stacy
Subject: RE: Message from Unknown sender (8479380009)

We should let the company know that it was determined that a REMS is not required at this time. I don't think we need to T-con unless the sponsor has questions. I don't think it matters how we tell the company and email is OK by me. I would run it by Sally (since Alice is on leave).

Dave Podskalny
Clinical Team Leader
Division of Neurology Products
WO-22 Rm. 4377
Phone 301 796-2778

From: Metz, Stacy
Sent: Wednesday, December 11, 2013 2:15 PM
To: Podskalny, Gerald
Subject: FW: Message from Unknown sender (8479380009)

Hi Dave,

This message below is from the Duopa sponsor (AbbVie) and after they submitted responses to our REMS questions a few months ago they offered to answer any questions we had or offered a tecon if we wanted one. I told them we would be discussing at our next team meeting and that we would be in touch when we had further information.

At this point, what should we tell them now regarding the REMS? I know we already have an answer, but we also have many other things to tell them regarding labeling and other patient info that will soon go in an IR.

Our next team meeting is Jan 7th if you just want me to tell him we will follow up after that.

Thanks!
Stacy

From: Cisco Unity Connection Messaging System [<mailto:unityconnection@fdsla04029>]
Sent: Wednesday, December 11, 2013 2:07 PM
To: metzs@fdsla04029
Subject: Message from Unknown sender (8479380009)

<< File: VoiceMessage.wav >>



NDA 203952

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Dear Dr. Kuntz:

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

We also refer to your amendments dated June 6, 2013, and June 15, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 28, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 28, 2014.

During our filing review of your application, we identified the following potential review issues:

DMPP Patient Labeling

- Information concerning the drug product should be included in the Medication Guide (MG). Information concerning the device should be included in the Instructions for Use

(IFU). For brevity and reading ease, avoid duplication of information across all patient labeling materials.

- To avoid duplication of information we recommend one IFU for this product (b) (4). The “daily information” should appear first, followed by a section towards the end of the IFU for “dose adjustment”. References can be made between the sections within one IFU if necessary.
- Patient labeling materials should meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006).
- Patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information. Do not use complex medical terminology.
- To enhance comprehension and readability, patient labeling materials should be written at a 6th to 8th 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.
- Patient labeling materials should be in fonts such as Verdana, Arial or APFont at font size 11 or greater to make medical information more accessible for patients with vision loss. We recommend Verdana 11 point font.
- Use bolded text instead of underlining and text boxes to highlight important information. Underlined text or text placed in a box is difficult to read for patients with vision loss.

Comments specifically for the IFU:

- The Instructions for Use (IFU) should be titled as such and appear at the end of the MG after the list of ingredients. The IFU and MG may be separate documents.
- IFUs are generally organized as follows:
 - Standard header
 - Bulleted list of all the supplies needed to complete the task, including an illustration of all supplies needed.
 - Patient instructions that are not sequential should be bulleted.
 - Patient instructions that are sequential should be labeled as “**Step 1, Step 2**” etc.
 - Figures should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related text. The figures should be labeled as “**Figure A, Figure B**” etc.
 - Within the figures there should be detailed labeling for each part of any device that the patient expected to become familiar with.
 - Refer to each figure at the end of each numbered step. For example, at the end of **Step 1**, say (**See Figure A**).

- Storage information as stated in the Prescribing Information (PI) should appear at the end of the IFU if the IFU will be a separate document. If you combine the IFU and MG, the storage information should appear in the MG only.
- Disposal information. If needles, syringes or injectable Pens are used to prepare or deliver the drug, disposal language should be consistent with the FDA “Safe Sharps Disposal” website language.
- Other pertinent miscellaneous instructions to the patient
- Manufacturer name and address
- If the IFU is a stand-alone document, add the statement “These Instructions for Use have been approved by the U.S. Food and Drug Administration.”
- If the IFU is attached to a MG, add the statement “This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.”
- “Approved” Month/Year

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Chemistry, Manufacturing and Controls

1. In your submission, you describe enteral tubes, extension tubes/sets, and tubing connectors/adaptors evaluated for compatibility during development and found suitable for LCIG administration. Please provide 510(k) #'s for all enteral tubes, extension tubes/sets, and tubing connectors/adaptors evaluated.

Combination Products Compliance Division

2. (21CFR 820.30) Please provide design control procedures that include the risk assessment for the finished product. Your design controls procedures should address: Design Inputs, Design Outputs, Design Review, Design Verification, Design Validation, Design Transfer, Design Changes, and Design History File as they relate to the final combination product.
3. (21CFR 820.50) Please provide purchase controls. The information provided should include your overall procedures controlling supplier qualification and controls over suppliers. It should also include information about supply acceptance activities such as physical checks, testing or other activities conducted to ensure the supplies received conform to your specifications. Your agreements with suppliers/contract manufactures related to the final combination product should be provided.

4. (21CFR 820.100) Please provide CAPA procedures.

You can use the guide listed below to determine what type of documents you should provide.

‘Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,’ (2003)

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>).

Additionally, CDRH Office of Compliance requires information regarding the assembly of the finished combination product (drug and delivery system), including packaging and final acceptance activities of the finished product in order to evaluate the safety and effectiveness of the finished product. This information should include the name, address, and FEI number of the facility or facilities involved in these activities.

Please confirm the location and FEI number of the Smiths Medical facility that manufactures the pump.

You should provide the information requested in Module 3.2.P.7 of the manufacturing section of the NDA.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. 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 granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Comment: Statements in Highlights do not need to be full sentences.

Do not include postmarketing adverse reactions in the Highlights Section.

2. White space must be present before each major heading in HL.
3. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
4. 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)”

We request that you resubmit labeling that addresses these issues by August 30, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ERIC P BASTINGS
08/08/2013

From: Metz, Stacy
To: [Pratt, Gregg A \(gregg.pratt@abbvie.com\)](mailto:gregg.pratt@abbvie.com)
Subject: CDRH Post Meeting Responses
Date: Monday, May 06, 2013 11:49:00 AM

Hi Gregg,

This email is to provide you with the CDRH Post Meeting Responses for Qs 28 and 29. Please see the following:

Question 28a:

Does the Agency agree that the update provided above on Human Factors interactions with FDA and summary of actions taken will address the CDRH comment?

CDRH Response:

The interactions were designed to clarify the deficiencies and next steps. CDRH has not reviewed the final report, and therefore, cannot agree that all of the CDRH comments have been adequately addressed.

Question 28b:

Are there additional HF studies that AbbVie should consider conducting beyond those presented in the NDA and, if so, is it possible to conduct these studies in parallel with the NDA review?

CDRH Response:

CDRH was informed that there would be a change in the Lock Level functionality, and has reviewed the use related risk analysis. Our review indicated that this modification would require additional Human Factors validation testing with at least representative users, and that this study should focus on capturing data on unanticipated/abnormal use. This recommendation was based on the risk analysis indicating that the Lock Level 1 introduces the risk of overdosing from potential use errors or potential abnormal use of the Prime button, which might be rare. If there are no other device-related modifications, we do not believe additional HF studies are needed.

Question 28c:

In addition, can the Agency provide an overview of how the Centers and Offices (CDER, CDRH, OCP, DMEPA) will interact during the review?

CDRH Response:

CDER will issue consults to CDRH for their consultative reviews on the device performance testing and Human Factors components.

Question 29a:

Can the Agency provide guidance on how product approval and 510(k) clearances will be coordinated?

CDRH Response:

Rather than awaiting 510K clearance of the NG and PEG tubing, you may submit a device master file to CDRH that will be referenced in the NDA.

Question 29b:

Can the Centers involved in approval and clearance (CDER and CDRH) notify AbbVie of any concerns regarding the 510(k) application submission plans in the preliminary comments prior to the Type A meeting?

CDRH Response:

The device will be approved in the NDA for use with your drug as a combination product. You may also submit a 510K for the device, which would be reviewed independently of the NDA for device clearance.

Best Regards,

Stacy

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

/s/

STACY M METZ
05/06/2013



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: March 14, 2013
Meeting Type: Type A
Meeting Location: White Oak Bldg #22, Room 1315
Application Number: NDA 203952
Product Name: Levodopa/Carbidopa Intestinal Gel
Received Briefing Package: February 14, 2013
Sponsor Name: AbbVie
Requestor: Jeremy McCumber
Meeting Chair: Eric Bastings, MD
Meeting Recorder: Stacy Metz, PharmD

Meeting Attendees:

FDA Attendees:

Eric Bastings, MD, Deputy Director
Gerald David Podskalny, DO, Medical Team Leader
Len Kapcala, MD, Clinical Team Leader (via phone)
Martha Heimann, PhD, CMC Lead
Charles Jewell, PhD, CMC Reviewer
Xiang Ling, PhD, Statistical Reviewer
Stacy Metz, PharmD, Regulatory Project Manager

External Attendees:

Janet Benesh, BSMT, Project Director, Neuroscience Development, R&D
Scott Brun, MD, Vice President, Pharmaceutical Development, R&D
Leslie Carter, PharmD, Sr. Director, Regulatory Affairs
Krai Chatamra, PhD, Global Clinical Director, Neuroscience Development, R&D
Jordan Dubow, MD, Associate Medical Director, PPD Program, R&D
Julie Garren, PhD, Sr. Director, CMC Regulatory Affairs
Mark Goldberger, MD, Divisional Vice President, Regulatory Affairs
Weining Robieson, PhD, Associate Director, Statistics, R&D
Ron Robison, MD, MS, Vice President, Regulatory Affairs, Medical Services, and R&D QA
Sybil Skinner-Robertson, BSc, Director, Regulatory Affairs
Andrew Storey, BS, Head, US and Canada Regulatory Affairs
Bo Yang, PhD, Global Head of Statistics, R&D

1.0 BACKGROUND

In a letter dated January 16, 2013, AbbVie Inc. requested a Type A Meeting to discuss the NDA Refuse to File Letter issued January 15, 2013. The Division's preliminary responses to the questions posed in the meeting package were electronically mailed to the sponsor on March 13, 2013. The following is a summary of the discussion of the questions at the meeting.

2.0 DISCUSSION

SUMMARY OF QUESTIONS AND FDA PRELIMINARY RESPONSES

Please refer to meeting package submission (2/14/13) for background to all questions.

Note to Sponsor:

We did not have the opportunity to review the response you sent in reply to our Preliminary Responses. Your responses, sent hours before the scheduled face-to-face meeting, did not leave sufficient time to review or discuss the additional comments internally. Although, we did not discuss or provided written comment for many of your additional responses, it does not indicate our agreement or acceptance of your additional responses.

Refuse to File Questions

Chemistry, Manufacturing and Controls (CMC) Questions

Question 1a:

Does the Agency agree that the Master Production Records when provided in the resubmission will meet the Code of Federal Regulations (CFR) requirements and resolve this RTF item?

Preliminary FDA Response:

Yes, the provided records in Appendix A meet the requirements to support filing.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 1b:

Does the Agency agree that the manufacturing process description provided in Appendix B provides sufficient detail to meet the CFR requirement and resolve this RTF item?

Preliminary FDA Response:

Yes, the manufacturing description provided in Appendix B has adequate detail to support filing.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 2:

Does the Agency agree that inclusion in the NDA of the executed batch records as described above will meet the CFR requirement and resolve this RTF item?

Preliminary FDA Response:

Yes, the described approach is adequate to support filing.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 3:

Does the Agency agree that the inclusion of the 6 Executed Batch Records for (b) (4) levodopa and carbidopa in the NDA resubmission will meet the CFR requirement and resolve this RTF item?

Preliminary FDA Response:

Yes, this is adequate to support filing.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Statistical Questions

Question 4a:

Does the Agency agree that the proposed format and content of the updated definition files as provided in the example in Appendix D give an adequate level of detail on how the derived variables were calculated and which variables in the raw data were used to derive the variables?

Preliminary FDA Response:

The description in Appendix D appears to be adequate to support filing. However, this is a matter of review.

Sponsor response:

The Sponsor would like to clarify what is meant by “a matter of review”. Does this comment mean that the content of the definition files could be an issue impacting the acceptability of the filing, or a matter for NDA review?

Meeting Discussion:

The Agency clarified that the information in the meeting package describes the Sponsor’s intentions; however, the files and information contained in the application are what will determine whether the application is suitable for filing.

Question 4b:

The Sponsor proposes that the updated definition file resolves this portion of the RTF issue and satisfies the Agency's request to adequately detail the definition of the analysis datasets. Does the Agency agree that this will resolve this portion of the RTF statistical issue?

Preliminary FDA Response:

The contents of the Define files appear to be adequate to support filing. However, this is a matter of review.

Sponsor response:

Please see response to Question 4a.

Meeting Discussion:

See meeting discussion 4a.

Question 4c:

Does the Agency agree that the proposed submission of the SAS codes including macros resolves this portion of the RTF statistical issue?

Preliminary FDA Response:

The proposed submission of the SAS codes and Macros appear to be adequate to support filing. However, this is a matter of review.

Sponsor response:

Please see response to Question 4a.

Meeting Discussion:

See meeting discussion 4a.

Clinical Questions

Question 5:

Does the Agency agree that the content and format of the completed draft literature review provided in Appendix E adequately resolves this RTF item?

Preliminary FDA Response:

- **The draft literature review planned for the NDA resubmission is no longer limited to adverse events of special interest (AESI). You have emphasized that this literature review will contain information from all types of studies. However, it is not clear if this literature review will also contain information derived from published case reports of one or more cases. Your literature review should be comprehensive and contain any published information on any safety issue/toxicity, including publications of case reports.**

Sponsor response:

The Sponsor would like to clarify that the literature review provided in the briefing book is inclusive of published case reports. We will ensure that this is made clear in the final literature review in the NDA resubmission.

Meeting Discussion:

No further discussion.

Question 6:

Does the Agency agree that these presentations of the coding dictionaries with VTs and PTs as described will satisfy the Agency's request for provision of a coding dictionary and resolve this RTF item?

Preliminary FDA Response:

You have not submitted examples of how your coding dictionaries will show:

1) verbatim terms (VTs) presented in alphabetical order on the left and the preferred terms (PTs) to which they were mapped on the right; or

2) PTs presented in alphabetical order on the left and all the respective VTs that were subsumed under each PT on the right. Your plan to submit the coding dictionary that we have requested appears to be adequate. All terms on the left should be presented in alphabetical order to permit the reviewer to locate a specific PT and then see what VTs are subsumed under each PT and to locate a specific VT and then see how that VT was mapped to a PT.

Sponsor response:

Coding dictionaries will be provided as outlined above. All terms on the left, whether VT or PT, will be presented in alphabetical order and mapped to the appropriate PT or VT.

Meeting Discussion:

No further discussion.

You have also noted that there were instances when a patient experienced a single adverse event, but had more than 1 (i.e., up to 4) PTs assigned to that specific adverse event, based upon the VTs associated with the adverse event. If a patient reported one single adverse event, but the event was coded to multiple PTs, this will falsely inflate the incidence of reported adverse events. When one adverse event is experienced, the adverse event should be coded under the single most appropriate PT to describe the event. For example, if a patient reported multiple VTs associated with a viral syndrome (e.g., general, respiratory, and gastrointestinal symptoms/signs) it should be coded to a single PT, viral syndrome. In such cases, we recommend that one or more of your physicians review and adjudicate the coding to a single PT based on an algorithm of VTs.

Sponsor response:

In order to differentiate an adverse event (AE) related to a device or procedure from those related to LCIG, more than 1 MedDRA PT was assigned to AEs that had the potential to be related to the device or procedure. For example, the VT "abdominal pain secondary to PEG-J procedure" was coded to the MedDRA PT of "abdominal pain" and was also coded to "complication of device insertion." Without this double coding, it would be difficult to assign cause of the abdominal pain, which could be related to either the procedure, or a symptom related to a drug or non-drug event. Conversely, if this event was only coded to complication of device insertion it would limit AbbVies ability to clearly identify the specific risks and medical consequences associated with the procedure or device.

As presented in the Type A meeting briefing package, there is only 1 incidence of a single VT that was coded to 4 PTs. In the case with 4 PTs, the VT of "pain and bleeding of stoma site; per GI doctor prolapsed and perhaps a bit of ischemic gastric tissue around stoma" was coded to 4 PTs of "gastrointestinal ischaemia," "gastrointestinal stoma complication,"

"post procedural haemorrhage," and "procedural pain." If this VT had been coded to only one term, "Gastrointestinal stoma complication" would seem most appropriate. This approach potentially over simplifies the event as a procedural complication, and provides no information on the specific medical ramifications of the event itself. The additional terms of pain and haemorrhage provide important medical context to this procedural event.

The viral syndrome example provided in the preliminary comments differs significantly from the complex case discussed above, which reflects the nature of the treatment system. Therefore, AbbVie proposes to maintain the coding convention as currently applied to provide this important level of granularity and to ensure that the specific risks of the LCIG system, consisting of drug and devices, are appropriately represented in the presentation of safety data.

Meeting Discussion:

The Sponsor will provide a list of limited number of VTs that may be mapped to more than one PT. The potential to inflate the number of PT exists in tables listing the overall number of adverse events but the increased representation of the PTs will diminish in the tables that list adverse event PTs as "Procedure Related" versus adverse events that are classified as "Drug Related."

Question 7a:

Does the Agency agree with the content and format for the requested incidence tables of TEAEs, SAEs, and TEAEs causing subject discontinuation by all dose categories for all trial periods?

Preliminary FDA Response:

- **We agree that the content and format (6 treatment/dose columns for controlled trial, and 3 treatment/dose columns for pooled, open-label trials) of the incidence tables of any TEAE, any SAE, and any TEAE causing study discontinuation appear to be appropriate for the 4 time perspectives (onset any time in whole trial, onset in titration period, onset in maintenance period, and onset in titration period and persisting > 7 days in the maintenance period).**
- **The content and format of the analyses of incidence of any TEAE, any SAE, and any TEAE causing study discontinuation described above for the 4 time perspectives should also be applied to each and every adverse event of special interest (AESI).
All subgroup analyses should also show the same content as described above but in a different format (e.g., showing 12 data columns for two treatments, 3 dose perspectives, and 2 subgroups on the same page in the controlled trial ; and showing 6 or 9 data columns for one treatment, 3 dose perspectives, and 2 or 3 subgroups on the same page in the pooled, open-label trials).**

Sponsor response:

AbbVie has proposed to provide the SAS tables for the subgroup analysis in the manner that has been described for the Controlled Clinical Study (and some pooled open-label analysis) in Non-RTF Item 17. The specific request in the RTF Letter states: "When feasible, present any dose and low dose and high dose on the same page. When this is not feasible, present information for any dose category for subgroup analysis on the same page, present dose analysis in one table then low dose versus high dose results together in another table"

In the March 5 teleconference with the Medical Reviewer, it was acknowledged that SAS cannot generate 12 columns of data, and the following format was discussed as the preferred SAS table presentation for these analyses:

low dose and high dose 8 columns:

INCIDENCE OF TEAE ANY TIME DURING TRIAL
BY GENDER - LOW/HIGH DOSE
(ACTIVE-CONTROLLED ANALYSIS SET)

SYSTEM ORGAN CLASS MEDDRA 14.0 PREFERRED TERM	LOW DOSE				HIGH DOSE			
	MALE		FEMALE		MALE		FEMALE	
	LCIG (N=16) n (%)	LC-ORAL (N=5) n (%)	LCIG (N=11) n (%)	LC-ORAL (N=10) n (%)	LCIG (N=8) n (%)	LC-ORAL (N=17) n (%)	LCIG (N=2) n (%)	LC-ORAL (N=2) n (%)
ANY ADVERSE EVENT	16 (100)	5 (100)	10 (90.9)	10 (100)	7 (87.5)	17 (100)	2 (100)	2 (100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
NEUTROPENIA	0	0	0	1 (10.0)	0	0	0	0
----- SUBJECTS WITH ONE OR MORE EVENTS	0	0	0	1 (10.0)	0	0	0	0
CARDIAC DISORDERS								
ATRIAL FIBRILLATION	0	0	0	0	1 (12.5)	0	0	0
ATRIAL FLUTTER	0	0	0	0	1 (12.5)	0	0	0
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (10.0)	0	0	0	0
TACHYCARDIA	0	0	0	0	0	1 (5.9)	0	0
----- SUBJECTS WITH ONE OR MORE EVENTS	0	0	0	1 (10.0)	1 (12.5)	1 (5.9)	0	0

and

- *all doses 4 columns:*

INCIDENCE OF TEAE ANY TIME DURING TRIAL
BY GENDER - ALL DOSES
(ACTIVE-CONTROLLED ANALYSIS SET)

SYSTEM ORGAN CLASS MEDDRA 14.0 PREFERRED TERM	MALE		FEMALE	
	LCIG (N=24) n (%)	LC-ORAL (N=22) n (%)	LCIG (N=13) n (%)	LC-ORAL (N=12) n (%)
ANY ADVERSE EVENT	23 (95.8)	22 (100)	12 (92.3)	12 (100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
NEUTROPENIA	0	0	0	1 (8.3)
-----	-----	-----	-----	-----
SUBJECTS WITH ONE OR MORE EVENTS	0	0	0	1 (8.3)
CARDIAC DISORDERS				
ATRIAL FIBRILLATION	1 (4.2)	0	0	0
ATRIAL FLUTTER	1 (4.2)	0	0	0
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (8.3)
TACHYCARDIA	0	1 (4.5)	0	0
-----	-----	-----	-----	-----
SUBJECTS WITH ONE OR MORE EVENTS	1 (4.2)	1 (4.5)	0	1 (8.3)

AbbVie will comply with the request from the medical reviewer to generate SAS tables in this format.

Additionally, AbbVie then proposed in the email dated 08 March 2013 that we could provide a limited number of hand generated 12 column tables. Specifically, 12 column tables were proposed for all subgroup analyses of TEAEs, SAEs, AEs leading to discontinuation, AESIs (5 categories) and other AE categories (falls, hypotension) evaluated for the entire treatment period (defined as "any time during trial"), reflecting the longest period of evaluation and the greatest number of events. This approach will represent approximately 70 tables (10 AE categories X 7 subgroup variables) that require hand generation based on our latest review of the requested analyses.

However, the preliminary meeting comments appears to request this 12 column format for all subgroup analyses, not just for the selected analyses as previously proposed.

The actual number of 12 column tables which would need to be generated to comply with this request for all sub-group analyses requiring this presentation is >400 tables. Notably, a significant number of these tables would contain information of limited to no discriminatory value.

In acknowledgement of this ongoing dialogue, AbbVie proposes to submit all the requested SAS generated tables as discussed during the March 5 teleconference, and the limited 12 column overview (any time during study) tables at the time of submission. Should further granular analysis be required during review, AbbVie would generate specific 12 column tables for sub-group analysis of interest as needed upon request.

Does the Agency agree that this is a reasonable approach to allow for a substantial review of the data?

Meeting Discussion:

The proposal to send the initial set of seventy 12-column tables for the subgroup analyses for the controlled trial results is acceptable. Additional tables may be requested, if necessary, and these may be presented as SAS generated 8-column on the first page and 4 columns on the next page format. The 6 or 9 column format is acceptable for the presentation of the treatment emergent adverse event information for pooled, open label safety data.

- **One of your planned tables proposes to present the incidence of patients who discontinued in the titration period but experienced a TEAE in the maintenance period (i.e., when the TEAE occurred within 30 days of taking last treatment but its onset would have been in the maintenance period if the patient had continued on treatment into the maintenance period). In all such cases, the TEAE should be included in the standard table showing TEAEs with onset in the maintenance period for patients treated in that period despite the fact that the patient had discontinued treatment in the titration period. If there are multiple such cases, then it may be appropriate to include a table that shows the incidence of TEAEs in the maintenance period for patients who discontinued in the titration period. However, if such cases are rare, it may be adequate to present the data as recommended for onset in the maintenance period but indicate as a footnote that the patient discontinued in the titration period.**

Sponsor response:

AbbVie is concerned that the assignment of this single subject to the maintenance period has additional consequences for how the other discontinued subjects in the controlled study are handled. If the rationale for adding this subject to the maintenance period is because they were technically at risk during this timeframe (maintenance defined as > 28days), we would then conclude that all the subjects who discontinued during titration phase should also be added back to the maintenance period as they too remained at risk for an additional 30 days. We are concerned that this methodology will artificially inflate the denominator and dilute any potential safety signal. This is of particular concern as the pivotal study is our only comparator study.

Therefore, we propose to not place the subject in the maintenance period but present it separately in its own table with the appropriate table. If agreeable to the Agency, we will footnote the Maintenance table to make reference to the individual subject table.

Meeting Discussion:

The Sponsor's proposal to only count the single patient who discontinued in the titration phase is acceptable.

SYSTEM ORGAN CLASS MEDDRA 14.0 PREFERRED TERM	LCIG			LC-ORAL			TOTAL (N=5) n (%)	P-VALUES
	LOW DOSE (N=2) n (%)	HIGH DOSE (N=0) n (%)	ALL (N=2) n (%)	LOW DOSE (N=3) n (%)	HIGH DOSE (N=0) n (%)	ALL (N=3) n (%)		
ANY ADVERSE EVENT	0	0	0	1 (33.3)	0	1 (33.3)	1 (20.0)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
FEMUR FRACTURE	0	0	0	1 (33.3)	0	1 (33.3)	1 (20.0)	
SUBJ WITH ONE OR MORE EVENTS	0	0	0	1 (33.3)	0	1 (33.3)	1 (20.0)	

Question 7b:

Does the Agency agree that this proposal resolves RTF Item 7?

Preliminary FDA Response:
 See response to 7a.

Sponsor response:
 Please see response to 7a.

Meeting Discussion:
 See meeting discussion for 7a.

Question 8a:

Does the Agency agree with the proposed dose conventions?

Preliminary FDA Response:

No. Instead of leaving the total daily levodopa dose as blank when there is some reason why that dose is not known, we request that you provide some indicator of the reason why the dose is not known. You could do this by assigning some specific coding letter for each specific reason (e.g., you have described 3 possible scenarios).

You have also noted that you planned to assign the last non-missing total daily levodopa dose to the date of resolution when a TEAE is ongoing at the data cut-off date but the patient is continuing treatment in your clinical program. We ask you provide some special indicator for such cases.

Sponsor response:
 No further discussion.

Meeting Discussion:
 No further discussion.

Question 8b:

Does the Agency agree that this proposal to provide treatment dose information in the electronic datasets will resolve this RTF item?

Preliminary FDA Response:

See response to 8a.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Non-Refuse to File Questions

Chemistry, Manufacturing and Controls (CMC) Questions

Question 9a:

Does the Agency agree that the data described above when provided will sufficiently describe the control of the drug substances' particle size?

Preliminary FDA Response:

Our concerns regarding control of the (b) (4) drug substances relate to all testing and manufacturing steps (b) (4)

(b) (4) In addition to the information described in the briefing package, we recommend inclusion of the following information:

3.2.S.2.1 (and 356h):

Identify the facility(ies) that will perform acceptance testing for the (b) (4) drug substances, including periodic full testing of all parameters listed on the certificates of analysis for vendor qualification.

3.2.S.4:

Provide the acceptance specifications for the drug substances and analytical procedures for any test parameters (e.g., residual solvents) that are not specified in the drug substance monographs.

Provide methods validation data to support any noncompendial analytical methods. If the HPLC related substances methods in the respective levodopa and carbidopa USP monographs are used to monitor impurities that are not specified in the monographs (e.g., (b) (4) in levodopa), provide validation data.

Provide certificates of analysis for drug substance batches used to manufacture drug product stability batches and the results of any acceptance testing performed by, or on behalf of, Abbvie.

The briefing package indicates that (b) (4) levodopa and (b) (4) carbidopa monohydrate conform to the respective USP monographs, plus additional testing (description, identification by IR, particles size, and microbial count). Clarify whether the (b) (4) drug substances are tested in accordance with the USP monographs and identify the facility(ies) responsible for testing these materials.

With respect to hold times for the (b) (4) drug substances, you provided hold time stability data on (b) (4) levodopa and carbidopa, but the carbidopa data did not include particle size data.

Sponsor response:
No further discussion.

Meeting Discussion:
No further discussion.

Question 9b:
Does the Agency agree that this proposal resolves Item 9?

Preliminary FDA Response:
See the above response. The adequacy of the provided data will be a matter for review.

Sponsor response:
No further discussion.

Meeting Discussion:
No further discussion.

Clinical Questions

Question 10a:
Does the Agency agree with the proposed presentation for subgroup analyses for outliers (PCS values)?

Preliminary FDA Response:

- **No. You have presented tabular formats for the controlled trial showing 6 data columns for 2 treatments and 3 dose perspectives and one member (e.g., male) of a subgroup consisting of 2 members (male, female). In such instances, the results of the other member (female) of the subgroup would be presented in another separate table. This approach is not conducive for reviewing and comparing results of the subgroup. The results for all treatments and all dose**

perspectives, for all members of the subgroup should be presented in a format that allows easy comparison of the subgroups (i.e., showing 12 data columns for two treatments, 3 dose perspectives, and 2 subgroups on the same page in the controlled trial; and showing 6 or 9 data columns for one treatment, 3 dose perspectives, and 2 or 3 subgroups on the same page in the pooled, open-label trials). You have indicated that it is possible to present tabular analyses with a tabular format of up to 12 columns of data.

- **All subgroup analyses should also be presented for 4 time perspectives (onset any time in whole trial, onset in titration period, onset in maintenance period, onset in titration period and persisting > 7 days in maintenance period).**

Sponsor response:

Please refer to response to Question 7a.

Meeting Discussion:

See meeting discussion for 7a.

Question 10b:

Does the Agency agree that the planned analyses when presented in the NDA resubmission will resolve Item 10?

Preliminary FDA Response:

See response to 10a.

Sponsor response:

Please refer to response to Question 7a.

Meeting Discussion:

See meeting discussion for 7a.

Question 11:

Does the Agency agree that the modifications to the patient narrative table as described above and shown in .Appendix G are acceptable to resolve Item 11?

Preliminary FDA Response:

- **No. The dose designated in the comprehensive listing of all patients with narratives should be the total daily levodopa dose at the time of onset of the adverse reaction prompting a narrative, [REDACTED] (b) (4) [REDACTED].**
- **We also have some additional comments/recommendations on the organization/format for the comprehensive listing of all patients with narratives:**
 - **Please organize the listing according to the following hierarchy of reasons for being on this list: death, non-fatal SAE, and TEAE causing study discontinuation. Thus, all the initial patients on this list in the first grouping will be associated with death, and the next grouping will be associated with a non-fatal SAE. If a patient has more than one reason for being on this list, insert the patient in the section according to the hierarchy recommended above here. All patients who are represented on a descriptive list only because of an AESI that was not associated with an SAE or study discontinuation should be in separate comprehensive, descriptive list (as in Appendix M) after this comprehensive, descriptive list (as in Appendix G) (see also DNP response to item/question # 21a).**
 - **We previously recommended (9/7/12) locating all narratives together in a single section of the ISS.**
 - **If you need to find space for the format of this comprehensive list of patients, you can delete the 5 columns on the right for the Type/Category of TEAE Prompting a Narrative and show this reason in a single column. When there is more than one reason, the additional reason(s) can be outlined in the same column in a row immediately below the first reason.**

Sponsor response:

AbbVie will organize the listing according to the following hierarchy of reasons for being on this list: death, non-fatal SAE, and TEAE causing study discontinuation.

AbbVie will provide the total daily levodopa dose at time of onset of AE prompting a narrative. Collection of data for dosing was based of design of study (blinded, safety, extension treatment, study duration). The controlled trial used a daily dosing diary, while the remaining trials recorded dose only on certain visits. We will use the same algorithm proposed in response to Item 8 for value of levodopa dose at time of TEAE onset

-If the total levodopa dose on day of onset was not recorded, the previous non-missing value will be carried forward

- For TEAE that occur before study drug start (AE on or after day of device placement by before study drug initiation), the total levodopa dose will be blank with a footnote indicate reason (pre-dose)*
- For TEAE onset that was after last dose of study drug (AE occurring within 30 days after cessation of treatment still considered TEAE), the total levodopa dose will be blank with a footnote indicating reason (post-dose)*

As requested two separate lists will be provided. The first list will be a comprehensive descriptive list (as in appendix G) followed by a second comprehensive and descriptive list which contains all patients who had an AESI that was not associated with an SAE or study discontinuation. Following both lists, the narratives will be presented in a single section of the ISS. The lists and the narratives following will be grouped by the hierarchy described above. Linking will be performed from the narrative to the eCRFs that we agreed to provide in the Pre-NDA Meeting (August 7, 2012) i.e. eCRFs for all subjects in Study S187-3-001/S187-3-002, and for Studies S187-3-003, S187-3-004, and S187-3-005, eCRFs for subject deaths, serious adverse events, and premature subject discontinuations. Thank you for the suggestions on how to obtain additional space for the format of the list as requested, we will make these changes.

Meeting Discussion:
No further discussion.

Question 12a:

Does the Agency agree with the following proposals?

- (1) maintain the post-text tables and listings TOC
- (2) provide a table numbering convention guide with key words, and
- (3) provide a TOT using abbreviated table titles categorized by key safety topics described above with key words and including hyperlinks directly to each table.

Preliminary FDA Response:

Dr. Kapcala in a teleconference with the sponsor on 3/5/13 has provided detailed comments/recommendations on improving the TOC by shortening the number of pages in the TOC, and making table names more concise, more descriptive, and consistent. Please refer to those comments/recommendations.

Sponsor response:

The Sponsor has noted DNP's recommendations from the teleconference of 3/5/13 to shorten the titles of tables in the table of contents and, for example, will remove repetitive and extraneous terms, underline key words and reduce the font. It is important to note that with the addition of approximately 1000 safety tables consequent to requests made by the Medical Reviewer, the table of contents will be longer than the one originally submitted; however, we will ensure it is as concise as possible. Based on feedback provided at the 3/5/13 teleconference, we will not provide the table numbering convention guide. Also, unless positive feedback is provided on the TOT, we will not provide this.

On 3/8/13 we sent the following email:

“... we have taken your advice to shorten the table titles in the TOC. This is reflected in the list of AE tables and prototypes. The font of the TOC will also be reduced to ensure that more table titles will fit on one page. Finally, key words will be underlined in the TOC. Please let me know if you need anything in addition in order to review these documents.” We would like to understand if the format that we provided for the TOC will address your concerns.

Meeting Discussion:
The plan appears to be acceptable.

Question 12b:
In totality, do these proposals resolve Item 12?

Note: AbbVie requests that if the Agency requires changes to the table numbering convention guide and the key safety topics or structure of the TOT, that these proposed changes be provided in the preliminary comments to facilitate discussion at the Type A meeting.

Preliminary FDA Response:
See response to 12a.

Sponsor response:
Please refer to response to Question 12a. Does the review team believe that the ToT will be useful in their review of the submission?

Meeting Discussion:
No further discussion.

Question 13:
Does the Agency agree that the proposal to present analyses by time for outliers will adequately resolve Item 13?

Preliminary FDA Response:

- **Yes, the analyses described in the briefing package appear to be acceptable.**

- **You have noted that because there were no measurements of clinical laboratory analytes during the titration period, associated tables will not be provided. You are also unable to provide “persistent” tabular analyses for clinical laboratory analytes because these data were not collected in the titration period.**
- **The subgroup analyses for all subgroups will also need to be conducted and submitted for all outlier analyses of all patients according to the 4 time perspectives (when applicable).**

Sponsor response:
No further discussion.

Meeting Discussion:
No further discussion.

Question 14:

Does the Agency agree that the tables provided in Appendix K in conjunction with the provision of the additional tables satisfying RTF Item 7, will adequately address this non-RTF item?

Preliminary FDA Response:

- **Yes, presumably, if the analyses are submitted as proposed here.**
- **These analyses (according to the 3 dose perspectives) should also be presented according to the 4 time perspectives.**
- **The subgroup analyses for all subgroups will also need to be conducted and submitted according to the 4 time perspectives.**

Sponsor response:
No further discussion.

Meeting Discussion:
No further discussion.

Question 15:

Does the Agency agree that the proposal to present the requested analyses by race will adequately address the Agency's concerns to resolve Item 15?

Preliminary FDA Response:

- **Yes, the analyses described in the briefing package appear to be acceptable.**

- **DNP reminds you that all analyses (according to the 3 dose perspectives) of race should be presented according to the 4 time perspectives and that each analysis of every time perspective should also be submitted for all subgroups.**

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 16a:

Does the Agency agree with this methodology and format for providing the total and percentage of TEAEs that were present at Baseline but became worse during treatment?

Preliminary FDA Response:

- **No, we recommend that your approach (methodology and format) for documenting adverse events present at baseline and worsening during treatment is not limited to adverse events associated with Parkinson's disease. For example, a patient may have had somnolence at baseline and this somnolence worsened during treatment. With your approach, it does not appear that somnolence would be captured in your confirmatory analyses. We recommend that you discuss with us an alternative approach if the number of adverse events present at baseline and worsening during treatment is too large.**
- **These confirmatory analyses should be conducted for the controlled trial and pooled, open-label trials.**
- **The table shown in Appendix J appears to be adequate. However, please provide hyperlinks to the CRF for each TEAE captured.**

Sponsor response:

The approach Abbvie has outlined in the briefing package does capture all AEs present at baseline and worsening during treatment, not just those limited to PD. As an example, the table provided in Appendix J lists insomnia, hypotension and REM Behavioral Sleep Disorder which are not specific PD symptoms, in addition to other symptoms that are PD related (eg. dyskinesia). Therefore the approach proposed by AbbVie is appropriately broad to capture events present at baseline which worsen during the study.

The tables requested in the RTF letter (which we assume are referred to in the preliminary response as confirmatory analysis), specifically 1) Number and percentage of subjects with worsening baseline TEAEs and 2) Worsening symptom TEAS reported as a number and percentage of all TEAEs, have been developed based on analyses conducted for both the

controlled trial and the open label trials as requested. The top-line results of these analyses, demonstrating consistency of reporting within the program, are presented below:

1) Number and percentage of subjects with worsening baseline TEAEs

Active Controlled study: 24/71 (34%) of subjects reported at least one worsening event

Pooled Open Label studies: 199/412 (48%) of subjects reported at least one worsening event

2) Worsening symptom TEAS reported as a number and percentage of all TEAEs.

Active Controlled study: 40/502 (7.7%) of all incidences of TEAS

Pooled Open Label studies: 539/4397 (12.3%) of all incidences of TEAEs

The provided example listing (Appendix J) captures all baseline AEs as well as all conditions identified in the medical history or specific PD related terms which could worsen to demonstrate that Investigators did, in fact, identify worsening of baseline AEs or baseline conditions as TEAEs.

As requested, terms in the example listing are hyper-linked to the same terms in the eCRF, for the Controlled Clinical study, since it was agreed at the pre-NDA meeting that all eCRFs for the pivotal study would be submitted.

Therefore AbbVie feels that we have responded completely once the confirmatory tables referred to above (Number and percentage of subjects with worsening baseline TEAEs and Worsening symptom TEAS reported as a number and percentage of all TEAEs) have been included in the resubmission.

Meeting Discussion:

The plan appears to be acceptable.

Question 16b:

Does the Agency agree with the proposed methodology to generate the in-text table (the requested example listing)?

Preliminary FDA Response:

See response to 16a.

Sponsor response:

Please see response to 16a.

Meeting Discussion:

See meeting discussion for 16a.

Question 16c:

Does the Agency agree that the in-text tables described adequately addresses the request for a sample listing?

Preliminary FDA Response:
See response to 16a.

Sponsor response:
Please see response to 16a.

Meeting Discussion:
See meeting discussion for 16a.

Question 16d:

Does the Agency agree that the new ISS Section 5.2.6 with the new in-text table and post-text tables described above will adequately address the non-RTF item of adverse events that were present at baseline and became worse during treatment that were counted as a TEAE?

Preliminary FDA Response:
See response to 16a.

Sponsor response:
Please see response to 16a.

Meeting Discussion:
See meeting discussion for 16a.

Question 17:

Does the Agency agree that the proposal to present subgroup analyses by treatment and dose will adequately resolve Item 17?

Preliminary FDA Response:

No. Based upon discussion and interactions with the sponsor subsequent to submission of this meeting briefing package, you have agreed to present all results of subgroup analyses for the controlled trial in 12 columns (2 treatments X 3 dose perspectives X 2 subgroups = 12 data columns) on the same page to facilitate subgroup comparisons. You also agreed that all results for subgroup analyses for the pooled, open-label trials will be presented in 6 or 9 columns page (1 treatment X 3 dose perspectives X 2 or 3 subgroups = 6 or 9 data columns) on the same page, depending on whether there are 2 or 3 subgroups.

Sponsor response:
Please see response to Question 7a.

Meeting Discussion:

See meeting discussion for 7a.

Question 18:

Does the Agency agree that the proposed subgroup analyses when presented in the NDA resubmission will adequately resolve Item 18?

Preliminary FDA Response:

No. The subgroup analyses should be presented according to the 4 time perspectives outlined previously for controlled trial (in 12 data columns on the same page) and for pooled, open-label trials (in 6 or 9 data columns on the same age) for:

- TEAEs
 - any TEAE
 - all AESI
 - falls PT search
 - hypotension/orthostatic hypotension PT search
- SAEs
 - any SAE
 - all AESI
 - falls PT search
 - hypotension/orthostatic hypotension PT search
- TEAEs causing study discontinuation
 - any TEAE
 - all AESI
 - falls PT search
 - hypotension/orthostatic hypotension PT search.

Sponsor response:

Please refer to response to Question 7a.

Meeting Discussion:

See meeting discussion for 7a.

Question 19a:

AbbVie agrees to perform the markedly abnormally low and high outlier analyses using the Agency's preferred values. Can the Agency please provide their preferred thresholds for the markedly abnormally low and high outliers (ISS terminology is PCS values) in the document provided in Appendix L in preliminary comments prior to the Type A meeting? Please note that this is the same document provided to the Agency to provide the outliers on October 26, 2011 and January 28, 2013.

Preliminary FDA Response:

We will provide a recommended table of outlier cut-off values for markedly abnormal/potentially clinically significant values in a separate table.

Sponsor response:

No further discussion

Meeting Discussion:

No further discussion.

Question 19b:

Does the Agency agree that the proposal for the handling of reference ranges and PCS values will adequately resolve Item 19?

Preliminary FDA Response:

Please response to 19a.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 20:

Does the Agency agree that the proposal for the presentation of and linking to narratives will adequately resolve Item 20?

Preliminary FDA Response:

No. DNP requests that linking to the CRF occur directly from each narrative to its respective CRF. It is not necessary to providing linking to the CRF from the comprehensive list.

Sponsor response:

The linking of eCRFs will occur directly from each narrative to its respective eCRF. Linking will be performed for the eCRFs that we agreed to provide in the Pre-NDA Meeting (August 7, 2012) i.e. eCRFs for all subjects in Study S187-3-001/S187-3-002, and for Studies S187-3-003, S187-3-004, and S187-3-005, eCRFs for subject deaths, serious adverse events, and premature subject discontinuations.

Meeting Discussion:

No further discussion.

Question 21a:

Does the Agency agree with the proposed format and content of the additional AESI narratives?

Preliminary FDA Response:

- **It is not necessary to provide any narratives for patients with any AESI that was not an SAE or a TEAE causing study discontinuation. Instead, we request that all such patients be included in a comprehensive, descriptive list as outlined in Appendix M, and that this list be located immediately following the comprehensive, descriptive list of patients with narratives (as outlined in Appendix G).**
- **We request that the total daily dose of levodopa on this list be the specific dose associated with each specific AESI, and not the mean total daily levodopa dose in the trial.**
- **We recommend that the format of the list outlined in Appendix M be modified to try to show many more patients on each page than are currently shown. The footnotes shown at the bottom (of Appendix M) do not need to be presented on every page of this list, but can be shown solely on the first page.**

Sponsor response:

Clarification of Question 21 and the Additional FDA Clarification

In the RTF letter received by the Sponsor on January 15, 2013, Item 21 states the following:

“Provide narratives for all patients with an AESI.”

In the first response received on March 13, 2013 to the February 14, 2013, Type A meeting briefing document, FDA stated the following regarding the Sponsor’s question to Item 21:

“It is not necessary to provide any narratives for patients with any AESI that was an SAE or a TEAE causing study discontinuation. Instead, we request that all such patients be included in a comprehensive, descriptive list as outlined in Appendix M, and that this list be located immediately following the comprehensive, descriptive list of patients with narratives (as outlined in Appendix G).”

FDA provided a further clarification on March 13, 2013, regarding the response to Item 21 as follows:

It is not necessary to provide any narratives for patients with any AESI that was not an SAE or a TEAE causing study discontinuation. Instead, we request that all such patients be included in a comprehensive, descriptive list as outlined in Appendix M, and that this list be located immediately following the comprehensive, descriptive list of patients with narratives (as outlined in Appendix G).

The Sponsor requests confirmation that narratives for any patient with any AESI that was not an SAE or a TEAE do not have to be included in the NDA resubmission.

Meeting Discussion:
No further discussion.

Question 21b:

Does the Agency agree that the proposal above will satisfy Item 21?

Preliminary FDA Response:
See response to 21a.

Sponsor response:
No further discussion

Meeting Discussion:
No further discussion.

Question 22:

Does the Agency agree that the proposal to present analyses for TEAEs suggestive of falls will adequately resolve Item 22?

Preliminary FDA Response:

- **No. DNP requests that analyses for TEAEs related to falls (as per outlined PT search list) and hypotension/orthostatic hypotension (as per outlined PT search list be submitted for the controlled trial (showing 6 column data format) and for the pooled, open-label trials (showing 3 column) according to the 4 time perspectives outlined previously for any TEAEs on each PT search list, for any PT in the search list designated an SAE, and for any PT in the search list designated as a TEAE causing study discontinuation.**
- **All the above outlined analyses for TEAEs suggestive of falls or of hypotension/orthostatic hypotension should also be conducted for every subgroup and presented in 12 data columns for the controlled trial and 6 or 9 data columns for the pooled, open-label trials (see also DNP response to item/question # 18).**

Sponsor response:
Please see response to 7a.

Meeting Discussion:
See meeting discussion for 7a.

Question 23:

Does the Agency agree that this proposal resolves Item 23 (clinical data requests)?

Preliminary FDA Response:

Yes. In addition, we will provide an outline of all requested safety analyses. We understand that you agree to submit these analyses in the format requested (as per 9/7/12 Pre-NDA meeting minutes outlining our requests for safety analyses).

Sponsor response:

We developed a complete list of safety analyses and table prototypes that address the requests for safety analyses identified in the 9/7/12 Pre-NDA Meeting Minutes, Refuse to File Letter and clarifications provided by DNP in the teleconference on 3/5/13.

In an email dated 3/8/13 we submitted to DNP a list of planned analyses (attached) and a number of prototypes to ensure that we addressed all of these requests:

“Attached is a list of planned analyses that we think will address all your requests from the meeting. Also attached are 15 prototypes of table shells. As you and I discussed on Wednesday, March 6th, can you please review and provide any comments you may have?” We acknowledge DNPs offer to provide an outline of all requested safety analyses. As stated above, we provided the outline of proposed ISS analyses on 3/8/13. We request FDA feedback regarding that outline at the meeting.

It is critical that we come to mutual agreement at the Type A meeting with the Division regarding the outline of analyses that AbbVie provided on 3/8/13 to permit resubmission of the NDA. It is important that we obtain a clear direction as soon as possible regarding all of the analyses that will be expected to permit filing of the NDA.

Meeting Discussion:

The requested safety analyses addressed by the attached list of tables are not filing issues but they facilitate the Agency’s review of the safety data.

The Controlled Substance Staff (CSS) and CDRH were not included in the January 16, 2013 meeting request from AbbVie to expedite scheduling of this meeting. The questions directed to CSS and CDRH (Questions #24-29) are not filing issues; therefore, CSS and CDRH did not provide written responses for these questions and their representatives will not attend the meeting.

Sponsor response:

The Sponsor acknowledges that the attendance of CSS and CDRH was not requested in the initial meeting request. We did however request participation at the meeting in the final briefing package. There are however some questions relevant to the resubmission that we would like to clarify. The Sponsor therefore requests that CSS and CDRH provide feedback on the briefing book questions in the final meeting minutes.

Meeting Discussion (Q24-29)

Only Q28c was specifically addressed. Please see meeting discussion for that question.

Note to Sponsor:

See “Additional Items Discussed” at the end of these meeting minutes.

Controlled Substance Staff Questions

Question 24:

Does the Agency agree that the provision of the available postmarketing narratives and source documents along with the literature summary and articles will address Item 24?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 25:

Does the Agency agree that the proposed content and format for the source documents for the 23 postmarketing events will provide adequate information to resolve Item 25?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 26:

Does the Agency agree that information proposed above will adequately address the risk of drug access from the cassette/pump, and the potential for direct patient contact with the gel to resolve Item 26?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 27a:

Does the Agency agree with AbbVie's proposal to evaluate customized reports from AAPCC to identify individual case narratives to request?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 27b:

Does the Agency agree that this proposal resolves Item 27?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

CDRH Questions

Question 28a:

Does the Agency agree that the update provided above on Human Factors interactions with FDA and summary of actions taken will address the CDRH comment?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 28b:

Are there additional HF studies that AbbVie should consider conducting beyond those presented in the NDA and, if so, is it possible to conduct these studies in parallel with the NDA review?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

Question 28c:

In addition, can the Agency provide an overview of how the Centers and Offices (CDER, CDRH, OCP, DMEPA) will interact during the review?

Preliminary FDA Response:

Sponsor response:

The RTF letter made reference to comments from CDRH regarding the analysis of the human factors studies that are potential review issues. Based on interactions with CDRH HFPMET personnel during Sept 2012, the Sponsor believes that the potential review issues identified in the preNDA meeting minutes have been suitably addressed. Please advise as to how the sponsor can obtain clarification from CDRH HFPMET personnel on whether the RTF letter refers to potential review issues beyond those previously described in the preNDA meeting minutes. A brief teleconference with CDRH HFPMET personnel would be preferred to assure questions from the Agency and the sponsor are suitably addressed.

Meeting Discussion:

The comments in the RTF Letter from CDRH and CSS were not filing issues. The review process is integrated, and interactive. The process engages review teams from other Agency offices and Divisions through out the review cycle.

Question 29a:

Can the Agency provide guidance on how product approval and 510(k) clearances will be coordinated?

Preliminary FDA Response:

Sponsor response:

As outlined in the information package, the sponsor will submit the first 510(k) application to CDRH in March.

Meeting Discussion:

No further discussion.

Question 29b:

Can the Centers involved in approval and clearance (CDER and CDRH) notify AbbVie of any concerns regarding the 510(k) application submission plans in the preliminary comments prior to the Type A meeting?

Preliminary FDA Response:

Sponsor response:

Please see previous response regarding CSS and CDRH feedback on briefing book questions.

General Questions

Question 30:

AbbVie respectfully requests that the Agency issue final meeting minutes less than 30 days from the conclusion of the Type A meeting. Can the Agency fulfill this request?

Preliminary FDA Response:

We plan to submit final meeting minutes within 30 days of the meeting, and sooner if possible.

Sponsor response:

No further discussion.

Meeting Discussion:

No further discussion.

Question 31:

Does the Division agree with this proposal (Resubmission Mechanism)?

Preliminary FDA Response:

In general, the proposed mechanism is acceptable. However, the ability to navigate within the resubmission is essential, and this will require review of the resubmitted application.

Sponsor response:

As described in the Type A Information Package, we plan to resubmit all changed files using “replace” as the eCTD leaf operation attribute. In addition, we plan to resubmit any files that contain hyperlinks to the replaced files, even if their content is not changing using “replace” as the eCTD leaf operation attribute. If the eCTD current view is used, or if the reviewer opens the resubmission sequence (0014), all hyperlinks will navigate to the appropriate file. However, if the reviewer opens the original (0000) sequence and clicks on a hyperlink, they may be directed to a file that has been replaced.

Is this resubmission mechanism acceptable? Is there a different mechanism that is suggested?

Meeting Discussion:

The plan appears to be acceptable.

Question 32:

Does the Agency agree with this proposal (Data Cutoff for the Resubmission)?

Preliminary FDA Response:

- **The majority of the long-term safety data should be included in the NDA. Under the current plan, the 120-day safety update would contain information for approximately 1- year of patient follow-up that is longer and larger than the safety information contained in the NDA. The cut-off date for the long-**

term safety database for resubmission of the NDA should be approximately 6 months before the resubmission date, similar to the cut-off date proposed in your original submission. You must include the bulk of the safety data with the NDA resubmission in order to allow a substantive review of the safety information to begin.

- We request that when the 4 Month Safety Update is submitted for patients continuing treatment in the open-label trial(s), the new cumulative updated data in the 4 Month Safety Update be presented along side the corresponding/respective data in the NDA resubmission. These side-by-side comparisons only need to be conducted for all the non-subgroup analyses and should also be presented according to the 3 dose perspectives so that the analyses will consist of 6 data columns.**

Sponsor response:

At the Pre-NDA meeting, AbbVie reached agreement with FDA on the plan for the submission of safety data for the NDA submission. This included the provision of at least 300 subjects with treatment exposure for 6 months and 100 subjects with exposure for 1 year. As of May 4 2012 all subjects were enrolled and had completed at least 6 months follow-up in the clinical trial program. The 120 day update will include all safety information available up to the date of resubmission. The following table summarizes the exposure that will be included the NDA and in the 120 day safety datasets. It demonstrates that a high percentage of safety information will be included in an NDA that has a May 4 2012 cutoff date. Specifically, 298 patients with LCIG exposure for at least a year are planned to be included in the filing, well exceeding the 100 subject database with this extent of exposure agreed upon with FDA at the preNDA meeting.

Duration of Exposure	Subjects exposed to LCIG	
	Cutoff (NDA)	to July 2013 (120 day update)
At least 6 months	350	350
At least 1 year	298	335

The NDA also contains 8 years of post-marketing data with (b) (4) patient-years of exposure. The safety profile in the clinical program is consistent with the post-marketing data presented in the NDA. Given that the vast majority of safety data will be included in the NDA with the May 4 2012 cutoff, and that the remainder of the safety data up until the

date of filing will be made available at the 120 day update, AbbVie proposes to keep the May 4 2012 cut-off date for the NDA.

Meeting Discussion:

The Sponsor proposes to include the majority of the safety information with the NDA resubmission. The plan is to resubmit the NDA in June or July 2013. They propose to retain the original NDA cut-off date of May 4, 2012, for the ISS. The 120-day Safety Update will include safety information for an additional 206 patient who continued treatment under open-label conditions for approximately 13-14 months. The Sponsor confirmed that enrollment is complete, and the 120-day safety update will not include information from new patients enrolled after the cut-off date for NDA filing. The 120 day Safety Update will present exposure and AE tables in 3 columns that show the number of patients or and events included in the NDA resubmission, another that shows the number of new events and patients included in the 120-day safety update and the last column will contain the new totals (NDA plus the 120-day update). The NDA resubmission will include updated information for deaths and Serious Adverse Events up to a cut-off date of 11/16/12 with the additional information place in the 120-day safety update using a cut-off date in July 2013.

Question 33:

Does the Agency agree with this proposal (Further Understanding AE Profile)?

Preliminary FDA Response:

Yes.

Sponsor response:

No further discussion

Additional Items Discussed:

Meeting Discussion:

The Sponsor is willing to remove the “Special Character” in the data files that prevent the files from being loaded into the Agency’s version of JReview. The Review Division will ask the Agency’s data management team to identify the special character and include the response in the Agency’s meeting minutes.

Post Meeting Note (conveyed to the sponsor via email on 3/20/13):

SAS datasets labels with unbalanced 'apostrophe' are in the current data submission, for example IPD dataset labeled "Diagnosis of Idiopathic Parkinson's.

The company has to remove all 'apostrophe' from SAS datasets labels.

Meeting Discussion:

Dr. Bastings will contact CDRH and ask if they can provide written responses to the Sponsor's questions #24-29 in the meeting package. If possible, these responses will be included in the Agency's meeting minutes.

Post Meeting Note:

CDRH will provide responses that will be sent separately from these meeting minutes.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

The sponsor provided analyses and handouts the morning of the sponsor meeting that were not discussed during the meeting and are not attached to these minutes. Please see March 27, 2013 electronic submission for the additional sponsor submitted information.

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

/s/

ERIC P BASTINGS
04/11/2013



NDA 203952

REFUSAL TO FILE

AbbVie Inc.
Attention: Jeremy M. McCumber, M.S.
Manager, Regulatory Affairs - PPG
1 N. Waukegan Road
North Chicago, IL 60064

Dear Mr. McCumber:

Please refer to your November 16, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levodopa-Carbidopa Intestinal Gel (LCIG).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d), for the following reasons:

Chemistry, Manufacturing and Controls

The process description for the drug product in this NDA is very general, lacking enough detail to review. This is a 505 (b) (2) application which requires a Master Production Record [see 21 CFR § 314.54 (a) (1) (i)]. In addition, an Executed Batch Record was provided, but only written in the Norwegian language where an English translation is required [see 21 CFR § 314.50 (g) (2)].

The following are required in order to address the above filing issues:

- Provide a proposed or actual Master Production Record for the complete drug product manufacturing process, from initiation through the filling and packaging process. Manufacturing equipment should be described. If this Master Production Record is not in the English language, provide the original record and the English translation. This should be referenced in section 3.2.P.3.3 as the description for the manufacturing process. Also provide a detailed manufacturing process description in section 3.2.P.3.3. Since you propose [REDACTED] (b) (4) as the first step in the drug product manufacture, the details of this operation should be included in the above required record and manufacturing process details.
- Provide the English translation of the Executed Batch Record in addition to the Norwegian version.
- Provide executed batch records for the [REDACTED] (b) (4) of levodopa and carbidopa.

Statistical

The definition file (define.pdf) for the analysis datasets does not contain information detailing how the derived variables were calculated and which variables in the raw data or case report form were used to derive the variables. You must submit a more detailed data definition file as well as the programming code (e.g., in SAS, including macros code) that was used to generate the analysis datasets.

Clinical

The summary of safety information is not sufficiently complete to permit a substantive review. In order to address this filing issue, you must provide the following:

- A comprehensive, integrative review of the published literature for all types of TEAEs (and not only for adverse events of special interest).
- A coding dictionary (as PDF files) showing how verbatim terms (VTs) for TEAEs were mapped to preferred terms (PTs) and also what VTs were subsumed under each PT. The “coding dictionary” consists of a list of all verbatim terms and the preferred terms to which they were mapped. Please submit the dictionary as a SAS transport file (.xpt) so that it can be resorted, and as a PDF document. The dictionaries should provide mapping of PTs in both directions (verbatim -> preferred and preferred -> verbatim) and show all items on the left in alphabetical order with the corresponding terms on the right (also see ICH E3-12.2.2).
- Analyses showing the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs causing subject discontinuation for all dose categories (any dose, low dose, and high dose) and for all trial periods (developing any time during the trial, developing in the titration period, developing in the maintenance period, and persisting from the titration into the maintenance period). Provide that information for controlled trials, open-label trials, and for pooled analyses of open-label trial data (also see ICH E3-12.3.3).
- The treatment dose information at the time of TEAE onset and resolution of TEAE in the electronic datasets (also see ICH E3-12.2.3).

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

During our review of your application, we identified the following issues that are not refuse to file items:

Chemistry, Manufacturing and Controls

The particle size of each (b) (4) drug substance appears to be a critical drug product quality attribute, so please include the following information in your application:

- A complete detailed description of the drug substance (b) (4) process, including a (b) (4)
- Enough stability data on (b) (4) drug substance to support its use to cover shipping conditions and maximum hold-time.
- Acceptance specifications for the (b) (4) drug substances at the site of drug product manufacture prior to use, including a description and validation of all analytical methods.

Clinical

- Please provide subgroup analyses for outliers for orthostatic vital signs, clinical laboratory analytes, and ECG parameters in controlled and open-label trials.
- Please add the dose of the assigned treatment to the comprehensive listing of all patients with narratives (also see ICH-E3-12.3.2).
- The table of contents (TOC) for post-text tables and listings appears to be excessively large (174 pages) and the table names are inconsistent, and lack important key words that identify their contents and the origin of the information. We would be happy to discuss specific concerns about the current TOC, and provide recommendations for renaming and restructuring the TOC.
- Please provide analyses by time (any time during the trial, titration phase, maintenance phase, and “persistent” abnormality from titration into maintenance phase) for all outlier analyses for orthostatic vital signs, clinical laboratory analytes, and ECGs parameters. Provide these analyses for all doses, low dose (< 1250 mg levodopa/day) and high dose (≥1250 mg levodopa/day). Present the analyses separately for controlled trial data, open-label trial data and pooled open-label trial data.
- Please present SAEs and TEAEs causing study discontinuation for pooled-open label trial data according to dose.
- Please conduct all subgroups analyses for race by comparing Caucasians (93 %) with Asians (6 %) in the pooled open-label trial data.

- To demonstrate that adverse events that were present at baseline but became worse on treatment were captured as TEAEs, please indicate the total number of TEAEs and the percentage of TEAEs for each trial, by treatment arm in controlled and open-label trials for new onset TEAEs (first onset during treatment) and adverse events present at baseline that became worse during treatment. Please provide several sample listings of adverse events that were present at baseline and became worse during treatment that were counted as a TEAE. Provide hyperlinks to each listed example to the corresponding CRFs, permitting the reviewer to understand your TEAE selection criteria.
- Please present all subgroup analyses of safety information according to study treatment and dose for controlled and open-label data. In addition, please provide a separate analysis by low dose versus high dose. When feasible, present analyses for any dose and low dose and high dose on same page. When this is not feasible, present information for the any dose category for subgroup analyses on the same page, present dose analyses in one table then low dose versus high dose results together in another table.
- Provide subgroup analyses for all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs causing study discontinuation according to dose for controlled and pooled open-label trial data. Your subgroup analyses for TEAEs was not comprehensive for all TEAEs but was limited only to adverse events of special interest (AESI).
- We do not agree with the reference values for clinical laboratory analytes including normal reference range and the proposed thresholds for markedly abnormally low and high outliers. We would be happy to provide recommendations regarding the reference values for outliers.
- Please present all narratives in a single location in the ISS and provide hyperlinks directly to narratives from ISS, from the comprehensive listing of all patients with narratives, and from the respective narrative whenever a reference to the narrative appears in the text of the ISS.
- Provide narratives for all patients with an AESI.
- Provide analyses for the incidence of TEAEs possibly suggestive of falls and hypotension/orthostatic hypotension, and TEAEs causing study discontinuation for:
 - All dose categories (any dose, low dose, high dose).
 - For all time categories (any time, titration phase, maintenance phase, and “persistent” abnormality from titration into maintenance phase),
 - For controlled trials, open-label trials and pooled data from open-label trials.
- Please refer to the meeting responses and minutes for the August 7, 2012, Type B meeting for the analyses of clinical data that should be included in the NDA submission.

Controlled Substance Staff

The literature describes a series of signs and symptoms called "dopamine dysregulation syndrome" (O'Sullivan et al. 2009; Giovannoni et al. 2000) that is associated with levodopa drug use in patients, and has features that are difficult to distinguish from or overlap with recreational drug abuse. In order to better understand this risk, you should provide the following:

- Case narratives or source documents supporting the text described in the eCTD Section 2.7.4.5.6 (Drug Abuse) statement: "However, there are rare postmarketing reports of abuse and dependence of medications containing levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state."
- The source documents of the 23 postmarketing cases identified using the Abuse Liability CMQ from the worldwide, Duodopa ^{(b) (4)} patient-treatment-year postmarketing database as described in your LCIG Abuse Potential Assessment.
- An assessment of the risk of accessing the drug directly from the current cassette/pump assembly, and any data regarding the direct contact effects of the gel.
- Information on the 20 to 40 intentional case exposures a year in the AAPCC National Poison Data Systems (NPDS) annual reports for "levo-dopa" drugs from 2005-2010.

Center for Devices and Radiological Health

Please refer to the meeting responses and minutes for the August 7, 2012, Type B meeting for comments from Center for Devices and Radiological Health regarding the analysis of the human factors studies that are potential review issues.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely yours,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
01/15/2013



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: August 7, 2012
Meeting Type: Type B
Meeting Location: White Oak Bldg #22, Room 1311
Application Number: IND 60,663
Product Name: Levodopa-Carbidopa Intestinal Gel
Received Briefing Package: July 10, 2012
Sponsor Name: Abbott
Requestor: Jeremy McCumber
Meeting Chair: Russell Katz, MD
Meeting Recorder: Stacy Metz, PharmD
Meeting Attendees:

FDA Attendees

Russell Katz, MD, Division Director
Gerald (Dave) Podskalny, MD, Clinical Team Leader
Len Kapcala, MD, Clinical Reviewer
Charles Jewell, PhD, CMC Reviewer
Martha Heimann, PhD, CMC Lead
Luann Mckinney, PhD, Nonclinical Reviewer
Sharon Yan, PhD, Biostatistics Reviewer
Alan Stevens, CDRH Reviewer (via phone)
Andre Jackson, PhD, Office of Clin Pharm
Larry Bauer, Rare Diseases
Stacy Metz, PharmD, Regulatory Project Manager

External Attendees

Janet Benesh, BSMT, Project Director, Neuroscience Development - GPRD
William Bracken, PhD, Director, Regulatory Affairs - PPG
Leslie Carter, PharmD, Senior Director, Regulatory Affairs – PPG
Krai Chatamra, PhD, Global Clinical Director, Neuroscience – GPRD
James Duhig, PhD, Manager, CMC Regulatory Affairs, Devices – PPG
Robert A. Lenz, MD, PhD, Divisional Vice President, Neuroscience Development – GPRD
Paula Martin, MPH, Associate Director, Regulatory Affairs – AN

Jeremy McCumber, Manager, Regulatory Affairs – PPG
Melodi J. McNeil, RPh, MS, Director, Regulatory Policy and Intelligence – PPG
Ahmed Othman, PhD, Assistant Director, Clinical Pharmacology and
Pharmacometrics-GPRD
Gregg Pratt, PhD, Director, Regulatory Affairs – PPG
Yili L. Pritchett, PhD, Research Fellow, Director, Clinical Statistics – GPRD
Robert F. Reder, MD, Group Medical Director, Product Safety – GPRD
Weining Robieson, PhD, Associate Director, Statistics – GPRD
Sybil Skinner-Robertson, Director, Regulatory Affairs – PPG
Andrew Storey, Head, US and Canada, Regulatory Affairs, PPG
Michael J. Walters, MS, Associate Director, CMC Regulatory Affairs – PPG
Katherine Widnell, MD, PhD, Medical Director, Neuroscience – GPRD
Katherine Wortley, PhD, Associate Director, CMC Regulatory Affairs, Devices – PPG (b) (4)



1.0 BACKGROUND

In a letter dated December 20, 2011, Abbott Laboratories requested a Type B Meeting to discuss the content and format of the planned LCIG NDA for the long term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)

(b) (4) The meeting was scheduled for March 2012 and the sponsor then asked to reschedule the meeting for August 2012. The Division's preliminary responses to the questions posed in the background package were electronically mailed to the sponsor on August 6, 2012. The following is a summary of the discussion of the questions at the meeting.

2.0 DISCUSSION

SUMMARY OF QUESTIONS AND FDA PRELIMINARY RESPONSES

Clinical Questions

Question 1:

Does the Agency agree that results from the combined single pivotal study are adequately robust to support the filing of the LCIG NDA for the proposed indication?

Preliminary FDA Response:

A single efficacy trial should be adequate to support filing of the LCIG NDA; however, this is pending review of the submission. The indication for the treatment of motor fluctuations in patients with advanced-stage Parkinson's disease [REDACTED] (b) (4) is subject to review. We may require modifications to the proposed indication following review of the NDA.

Sponsor Pre-Meeting Response to our Preliminary Comment:

Abbott acknowledges the Agency's response. We would like to understand what type of modifications to the indication might be required.

You should clearly demonstrate the basis for establishing that every patient enrolled in your two pivotal trials (that were combined) had been [REDACTED] (b) (4). More specifically, you should clearly document why every patient enrolled met the protocol specified requirements for enrollment in the pivotal trials and [REDACTED] (b) (4).

Sponsor Pre-Meeting Response to our Preliminary Comment:

Abbott acknowledges the Agency's response and will include the requested information in the NDA.

Meeting Discussion:

If approved, the indication for LCIG will depend on our review of the clinical trial information. The proposed indication for "long-term treatment of motor fluctuations in patients with advanced [REDACTED] (b) (4) Parkinson's disease [REDACTED] (b) (4) contains several assumptions that must be supported by the information submitted in the NDA. The Agency also reminded the sponsor during the meeting held on January 18, 2011 that it might consider [REDACTED] (b) (4) on the review of the application.

Question 2:

Does the Agency agree that the overall safety exposure of LCIG for the indicated population is adequate to support the filing of the NDA?

Preliminary FDA Response:

The overall exposure of LCIG for the indicated population appears to be adequate to support the filing of the NDA.

Meeting Discussion:

No further discussion at the meeting.

Question 3:

On the basis of the safety data provided in this information package, does the Agency agree that the adverse events of special interest as identified are appropriate?

Preliminary FDA Response:

You should present information about adverse reactions of special interest including the frequency of procedure- and device-related complications/adverse reactions according to general categories and according to specific subcategories such as infection(s), peritonitis, bleeding/hemorrhage, perforation, and various gastrointestinal complications (e.g., pancreatitis, obstruction, etc.). In addition, you should present information (including the frequency) about other “class related” adverse reactions (i.e., melanoma, impulsive/compulsive behavior(s), “sleep attacks”/sudden onset of sleep).

Sponsor Pre-Meeting Response to our Preliminary Comment:

The information requested will be provided in the NDA.

Multiple published reports suggest a potential treatment emergent polyneuropathy associated with LCIG. It has been suggested that the polyneuropathy may be related to certain nutritional deficiencies (e.g., vitamin B6 , B12, etc.). Can you test blood and urine from participants in their clinical trials program for various nutritional analyte levels to determine if this polyneuropathy is related to a specific nutritional deficiency?

Sponsor Pre-Meeting Response to our Preliminary Comment:

Our currently ongoing clinical trials monitor for B6, B12, folate, MMA and homocysteine in blood every six months. Are there additional markers of nutritional status that FDA would recommend to measure in blood and urine samples?

Meeting Discussion:

- *The total number of published reports describing patients who developed polyneuropathy after starting treatment with LCIG continues to increase. Nutritional deficiency is one possible explanation for the neuropathy. The serum testing for B6, B12, folate, MMA and homocysteine are sufficient to monitor for nutritional deficiency. We believe that it is important to gather as much information as possible regarding the cause of the polyneuropathy, any attempted interventions and patient outcomes.*
- *The Sponsor stated they did not collect pre-treatment data for these biomarkers systematically in these ongoing trials and that the data would mainly show results for markers during treatment.*
- *The Agency asked the Sponsor to present its analysis of the safety data including its assessment of the frequency and severity of PEG related complications in patients treated with LCIG compared to patients who received PEG tubes for other indications. The sponsor noted that it does not believe than the risk for complications related to the PEG during LCIG treatment was greater than the risk of the PEG for other indications.*

Question 4:

On the basis of the data provided, and the clinical relevance of the endpoint, can the Agency provide further clarification on whether change from Baseline to Week 12 in normalized "On" time without troublesome dyskinesia (b) (4)

(b) (4) could be considered suitable for inclusion in the USPI?

Preliminary FDA Response:

We would consider including information describing an increase in "on" time without troublesome dyskinesia in the label; however, the decision regarding whether to include this information in label and its' location in the label will depend on our review of clinical trial data. Inclusion of information on (b) (4) is not suitable for inclusion in the label based upon the reasoning that we outlined previously in our recommendations communicated (11/11) for you Statistical Analysis Plan (SAP). (b) (4)

Meeting Discussion:

No further discussion at the meeting.

Nonclinical Question

Question 5:

Does the Agency agree that these nonclinical data will meet the Agency's expectations as discussed at the 18 January 2011 meeting and allow for adequate review? Does the Agency agree with the placement of the information within the eCTD structure, as outlined?

Preliminary FDA Response:

The adequacy of the information intended to support the specification limits for hydrazine, (b) (4) and (b) (4) will be a matter of review. The proposed placement of this information in the NDA appears acceptable; however, a summary document with hyperlinks to all information on these impurities should be provided in Module 4.

Meeting Discussion:

No further discussion at the meeting.

Chemistry, Manufacturing and Controls Questions

Question 6:

Does the Agency agree that the stability protocol as summarized and the data Abbott will provide in the NDA could be considered sufficient to support the shelf-life of 24 months?

Preliminary FDA Response:

The protocol appears adequate to support long-term storage up to 24 months. The shelf-life assignment will be based on our review of the long-term stability data provided in the submission. Since this is a frozen product, no extrapolation will be used to establish the shelf-life.

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

No further discussion is required.

In addition, if the 24-month time point data is not available at submission, we recommend providing data for the longest time point at -20°C storage followed by the 5°C storage data.

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

If the -20° C and subsequent 5° C storage data become available during the review period, can the Sponsor submit the updated information with the 120-day safety update and obtain the proposed shelf life?

Meeting Discussion:

The sponsor plans to submit 2-month stability data at 20C with the NDA. However, they plan to submit the stability data for product stored at 5°C when they submit the 120-day safety update. The Agency may review information submitted after the filing date, if resources allow but they cannot guarantee they will be able to review the amendment within the same review cycle. The stability information for product stored at 5°C should be included in the NDA submission.

Preliminary FDA Response

Since this is a drug product stored under frozen conditions, you are advised to do a stressed stability study that would cover several freeze-thaw cycles, in case there are occasions when the drug product is allowed to thaw during the storage period. Evaluation should include monitoring of desired physical properties of the gel (e.g., homogeneity, viscosity, particle size, etc.).

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

The following table outlines the temperature cycling studies and analytical testing that has been conducted and is planned to be submitted in Module 3. Particle size is a drug substance specification and is not tested as part of the drug product specification, thus it is not included in the testing as described below.

(b) (4)



(b) (4)

Do these studies meet the Agency's expectation?

Meeting Discussion:

The Agency expressed concern that particle size growth, if it occurs, could be detrimental to product performance, and it is possible for this to occur with freeze-thaw cycling. The Sponsor did not assess particle size during this study and the data is not currently available. The Agency considers that particle size is an important physical attribute for the proposed product. The Sponsor should provide a justification for relying on a surrogate test for particle size such as visual examination. The Sponsor should also submit that data to support the use of the proposed surrogate with the NDA. If the Agency determines that the use of the surrogate is not justified, the Sponsor may need to perform additional studies.

Question 7:

Does the Agency agree that the simulated-use compatibility study design provided is sufficient to support the submission of the NDA?

Preliminary FDA Response:

We recommend that you conduct this study using samples of each unique set of tubing to be used with the product. This should include all tubing for both stoma based delivery and nasal tube based delivery. We also recommend including hydrazine in the degradation products testing for these studies.

Sponsor Pre-Meeting Response to our Preliminary Comment:

The Sponsor will conduct the simulated-use compatibility study to address the impact of the tubing on the drug for all tubing recommended for use with the product, including both stoma based delivery and nasal tube based delivery. The information will be provided in Module 3.

The Sponsor did not test for hydrazine during the simulated-use compatibility testing study as we have a good correlation between the formation of (b) (4) and hydrazine in our drug product. Due to the study design and the current analytical methodology available for hydrazine testing, the number of samples to be tested would have impacted the accuracy of the hydrazine to (b) (4) Carbidopa degradation levels. Abbott uses the accelerated stability data generated for hydrazine as the worst case degradation.

The Sponsor proposes to calculate the amount of hydrazine from the (b) (4) results in the simulated-use compatibility studies and report the calculated values in Module 3.

Does the Agency agree with this proposal?

Meeting Discussion:

The Agency agreed to review the Sponsor's data supporting the proposed method of calculating the amount of hydrazine present in the drug product by measuring the amount of (b) (4). The data and rationale for relying on (b) (4) levels obtained from the simulated-use-compatibility studies must be included in the NDA. If the Sponsor's proposed methods are not justified, additional studies may be needed.

The compatibility study with all recommended tubing should address the impact of the drug product formulation on the tubing itself as well as the effect of the tubing on the drug product. It is also advised that you provide recommendations for how often the tubing needs to be changed, based on the data from in-use studies for the recommended duration of tube use.

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

The Sponsor will provide data regarding the assessment of the impact of the tubing on the drug product as part of the in-use compatibility study and will provide this in the application.

The Sponsor is proposing not to conduct a drug on tubing compatibility because the impact of the drug on the tubing is considered to have a low probability of risk. The rationale is as follows.

The drug product is similar in characteristics of common nutritional/food products. The drug product is composed of approximately (b) (4) water and (b) (4) drug substance and inactive ingredients (b) (4). Levodopa and carbidopa monohydrate are related to tyrosine, a polar amino acid, and the inactive ingredient, carmellose sodium, is a soluble polysaccharide commonly used in food products as a thickening agent. Based on the composition, the drug product is expected to perform as other aqueous media.

The recommended tubing materials are suitable for enteral delivery and use with common enteral fluids, including aqueous media. These materials are consistent with 21 CFR 177.2600 "Rubber articles intended for repeated use" or specific Food Contact Substance (FCS) Notifications. In practice, users are instructed to infuse the drug product for up to 16 hours per day. The users are also instructed to flush the implanted jejunal tube with potable water daily at end of infusion, therefore, contact with the drug product is considered temporary. It is expected that due to the above mentioned drug product characteristics, repeated contact with LCIG to tubing would pose a non-significant risk for loss of integrity. This risk is similar to tubing that maintains integrity for repeated use in food contact applications.

The data from the clinical program (patient exposure ~580 patient years) represent the long term impact of the drug product on the tubing, more so than an in-use compatibility study could do. One device event that could be attributed to tube integrity is device occlusion. Over time in the clinical program, the number of device occlusions was shown to decrease. This finding suggests that the long-term use of the drug product has not been associated with impaired function of the tubing. Additional assessment of device events that could be related to tube integrity is ongoing.

The Sponsor has determined that the enteral tubing does not need to be replaced at a fixed interval of the clinical trial subjects who underwent tube replacement, the majority (>95%) were not associated with Serious Adverse Events. Subjects recognized that they were experiencing a tubing related device event as they presented either with decreased clinical efficacy or visible tube displacement. Events such as these would drive tube replacement, rather than an arbitrarily defined replacement time period that may result in unnecessary procedures in this patient population. The Sponsor is in the process of continuing this assessment and will provide the final results in the application. Based on these clinical trial findings, and the tubing exposure collected in the clinical studies, the Sponsor will make an appropriate recommendation regarding a need for tube replacement in the NDA.

Does the Agency agree with the Sponsor's drug on tubing assessment and tubing replacement approach?

Meeting Discussion:

The Agency understands the tubing is generally intended for long-term use (possibly several years). The decision to replace the PEG is often determined by when the tube becomes non-functional due to obstruction or incorrect positioning of the tube which may present as loss of efficacy. However, the properties of the degraded tubing, due to long-term continuous exposure of drug product (~ 16 hrs. per day) will need to be addressed in some fashion. The Sponsor's justification supporting the acceptability of long-term delivery of LCIG through the recommended tubing system(s) is based on ~580 years of patient exposure experience. The Sponsor should define how they counted the exposure experience in detail (how the pt-yrs accrued). In addition, the Sponsor must translate patient exposure experience into data and present analyses to support their assertion that degraded tubing will not interfere with drug product performance and safety with time. Otherwise, testing of aged tubing with in-use experiments for long durations (simulating actual use) may be required to support the proposed use of this tubing for long durations. The Sponsor must design these experiments and that may possibly be done in parallel with actual use (post approval commitment).

The recommended jejunal tubing is only intended to be used with this LCIG product and that other drugs will not be delivered via this tubing. The Agency also asked the Sponsor to address concerns about co-administration of tube feeding products with LCIG because of the competition with levodopa for active transporter binding sites by protein (neutral amino acids) contained in feeding solutions. The Sponsor clarified that the PEG has two ports, a gastric port and a jejunal port. The gastric port could be used for delivery of other medications; however, this does not address the potential loss of efficacy caused by this

drug-food interaction caused by administering simultaneous gastric tube feeding and jejunal LCIG.

Additionally, you are reminded of the need to have performed extractables/leachables studies on all recommended tubing.

Sponsor Pre-Meeting Response FDA Preliminary Comment:

Extractable/leachable studies have been conducted for the primary container closure system (cassette). Abbott will provide extractables data as part of the bio-compatibility requirement per ISO 10993 for the tubing that will be submitted. Leachables testing will be conducted as necessary based on the results from the extractables data. This tubing includes the Abbott branded NJ, PEG, and PEG-J, and these data will be provided in the 510k applications. For the tubing that will be recommended that is already cleared for use in the US, Abbott will work with the vendors to determine if the bio-compatibility testing has already been completed. Abbott will provide documentation regarding the testing that has been completed. This information will be available no later than the 120-day safety update.

Does the Agency agree with this proposal?

Meeting Discussion:

The Agency indicated that the reminder of the requirement for extractables/leachables study for all tubing types was a proactive comment, since the sponsor did not address this in their pre-meeting package. The Sponsor's approach to providing the information is reasonable. It will be reviewed in connection with CMC and device aspects of this application.

Post meeting comment:

It is understood that the extractables data for the Abbott branded tubing will be provided in the 510k submission. To assist in the review of the drug product, and to support drug product labeling recommendations, we request that a summary of the results be submitted to the NDA.

Combination Products Question

Question 8:

Does the Agency agree with the plan outlined and plan for the initial filing and subsequent maintenance of the device components in the NDA?

Preliminary FDA Response (Provided during the meeting):

The plan is acceptable. Please note that the cross-labeled device submitted through 510(k) will not be able to be cleared prior to approval of the NDA and will require coordination in terms of timing of the submission and clearance process.

Meeting Discussion:

No further discussion at the meeting.

Human Factors Question

Question 9:

Does the Agency agree that the scope of the human factors studies conducted and the results provided in the summary of the studies support the filing of the NDA for LCIG?

Preliminary FDA Response (Provided Post Meeting):

You stated that there are no safety critical tasks (i.e. those that would result in death, serious/permanent injury or disability to the user) (page 477). Therefore, the use failures, close calls, and operational difficulties identified across all tasks performed by both user groups (healthcare provider, and patients) are not safety-related. However, we believe that any tasks where task failures/use errors can result in patient/user harm (i.e. patients not receiving their therapy, over/underdosing, dyskinesia, loss of mobility, pain/discomfort) should be considered as critical. Therefore, all "essential" tasks identified for the study should be considered safety-critical tasks due to their potential negative clinical impact associated with inadequate task performance.

Our review of your data analysis indicated that there are some areas of concern:

Performance Failures

1. Pump Program Tasks

- a. Task failure was reported when an HCP changed Continuous Rate when attempting to change Morning Dose volume. This HCP indicated that she recognized that she had input the wrong value but did not correct, and was subsequently confused by the value that she entered. This user did not correct here error but indicated that she would have her colleague check the values. It is possible that in actual use, users may receive assistance from other staff. However, we are concerned that failure to properly program the device can lead to patient harm, and in this case, over dosing/patient dyskinesia.*

2. Morning Procedure

- a. Task failures were reported when several patients unable to performing tasks to connect either the medication cassette to the pump or removing the red cap from the cassette tube before attaching to PEG-J Tube. In one instance, the patient tried multiple times and was not able to determine the correct orientation of the cassette for attachment. You indicated that the risk mitigations are patients will have access to the oral therapy, and that the pump will alarm due to blockages or obstructions. However, the pump did*

not alarm due to inadequate fill volume in the pump to generate sufficient pressure for the alarm threshold. These failures indicated that patients were unable to connect the different system components. Additional, since the alarm was not generated consistently, it remains unclear if users would respond to alarm appropriately.

- b. Task failure was reported on one HCP who appeared to close clamp when reading task to open clamp in IFU. The risk mitigation indicated that pump alarm would be generated due to blockages or obstructions. However, it was unclear if the alarm was generated during the testing and if users responded to the alarm appropriately.*
- c. Task failures were reported on several HCPs, who failed to press the Morning Dose and Run to deliver dose. This could lead to under-dosing. It is unclear if existing mitigations were effective. The labeling (b) (4),*

Some close calls were also reported associated with the Morning Dose option. Users were reported to be confused. However, it was not clear if users were able to take corrective action.

3. Changing the Cassette

- a. Task failures were reported on multiple patients and HCPs on connecting and operating the cassette tubing, the red cap, the PEG-J. It was not clear why alarms were not generated and whether users took appropriate actions.*

4. Evening Procedure Task

- a. Task failures were reported on multiple patients and HCPs on clamping the cassette tube, reconnecting the red cap, twisting the PEG-J, and flushing the PEG-J. It was not clear how existing mitigations were effective in reducing the potential failures/errors.*

Operational Difficulties

Multiple users experienced operational difficulties across all user tasks. However, it is unclear how users overcame the difficulties and whether the device and its labeling/IFU influenced their action.

The study results showed that inadequate use performance that could potentially lead to patient/user harm (i.e. patients not receiving their therapy, over/underdosing, dyskinesia, loss of mobility, pain/discomfort). Furthermore, it appears that there are alarms that are critical and inadequate use performance could lead to patient harm. However, the testing did not appear to focus on tasks to demonstrate that users can recognize critical alarms, and take appropriate action to address the alarm conditions. Please address the concerns outlined above, and include in your discussion how the device design, and its labeling/Instructions for Use effectively minimized failures. Alternatively, we request that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

When you perform additional testing to demonstrate the adequacy of your mitigation efforts, please ensure that you include representative users, prioritize the testing in accordance with the potential clinical impact of use error and includes adequate subjective assessment from study participants so that any errors that do occur can be understood in terms of their cause from the perspective of the users. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:

*<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>*

Risk Management Questions

Question 10:

Does the Agency agree that the items represented above are the key risks to be managed for the LCIG System?

Preliminary FDA Response:

Agreement on the key risks to be managed depends on review of the submission.

Meeting Discussion:

No further discussion at the meeting.

Question 11:

Would the Agency provide comments on the draft US RMP provided?

Preliminary FDA Response:

It is premature for the Agency to comment on the draft US RMP. We will not be in a position to discuss this until the review of the submission is underway, and specifically, beyond the mid-cycle point.

Meeting Discussion:

No further discussion at the meeting.

Question 12:

Would the Agency agree to an ongoing dialogue between Abbott and the Agency, including the Division of Risk Management, to discuss the design of the LCIG US RMP during the NDA review process?

Preliminary FDA Response:

Without having reviewed the submission, it is not possible to have a dialogue regarding the RMP. Such a dialogue will most likely not begin until the review is beyond the mid-cycle point.

Sponsor Pre-Meeting Response FDA Preliminary Comment:

Abbott would like to reiterate our interest in initiating these discussions as early as possible in the review cycle to ensure all issues can be addressed within the first review cycle. No further discussion is required at this time.

Meeting Discussion:

No further discussion at the meeting.

Regulatory Questions

(See Meeting Package Questions for additional background information for this section.)

Question 13:

Does the Agency agree with this proposal?

Preliminary FDA Response:

The analysis data should require limited programming without losing all the important and relevant variables to allow us to verify the data. All variables need to be properly labeled. Variable codes need to be provided. Please also refer to *CDER Data Standards Common Issues Document* and *Study Data Specifications* <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm> in preparing data.

We require that you conduct and submit the additional efficacy analyses that were requested (11/30/11) when we provided comments on your Statistical Analysis Plan (SAP). We have reviewed your SAP that was revised after our feedback and it appears that some of the analyses we requested were not incorporated in your revised SAP. Please incorporate the following analyses (for the primary efficacy endpoint and

secondary efficacy endpoints) in your SAP and conduct and submit them in your NDA.

Sponsor Pre-Meeting Response FDA Preliminary Comment:

As per the SAP submitted 08 Dec 2011, we have performed LOCF and MMRM analyses for each of the variables the Agency suggested, which are:

- Absolute change in PD diary data: "Off" time, "On" time without troublesome Dyskinesia (DK), ("On" time without DK and "On" time with non-troublesome DK), "On" with troublesome DK, and Asleep.
- Percent change in normalized and absolute change for each of the variables mentioned above.

These analyses are described in the SAP V4 in pages 44-45.

A detailed description of the variables will be provided in the NDA as requested.

Present all efficacy analyses at each visit over time from baseline until the last visit.

- **Present all efficacy analyses separately, including observed data (i.e., all collected efficacy data without any imputation) at any post randomization/treatment time) and for "non-resistant" patients (i.e., patients who did not meet the enrollment requirement/criteria of inadequate control of Parkinson's disease when "non-resistant" patients represent 20 % or more of either respective treatment group - LCIG or oral LD/CD).**

Sponsor Pre-Meeting Response FDA Preliminary Comment:

Out of 66 subjects included in the PD symptom diary analysis, 61 subjects had three valid diary data and 5 subjects had two valid diary data at Week 12. As such, there was no need to apply the imputation specified in SAP V4 (page 42) for any of the diary variables.

There is only one subject in the "non-resistant" subject population; as such, the requested analysis could not be conducted. The analyses for the "Resistant" population were conducted as specified in the SAP V4 and the data will be presented in the Clinical Study Report.

- **Conduct and present sensitivity analyses for all primary and secondary efficacy endpoints:**
 - 1) **by including the average daily dose of rescue therapy throughout the trial in the ANCOVA model.**

2) by using the average baseline data (i.e., Baseline Observation Carried Forward-BOCF) to replace the actual daily data collected on days when patients received rescue therapy.

3) by following/applying your proposed algorithm for calculating average categorical diary data when diary data are missing.

Sponsor Pre-Meeting Response FDA Preliminary Comment:

There are a total 46 efficacy variables, including 27 related to the PD symptom diaries and 19 from other instruments. The Sponsor is concerned about multiplicity issues that may arise in performing these additional analyses beyond the primary efficacy endpoint for which the analyses requested in item 1 and 2 above have already been performed. Abbott proposes to perform those analyses on normalized and absolute diary variables, but not on percent change variables or on other efficacy variables not obtained from PD symptom diaries.

Does the Agency agree with this proposal?

- **Please analyze the change from baseline for Part IV of the UPDRS as a secondary efficacy endpoint (a new request).**

Sponsor Pre-Meeting Response FDA Preliminary Comment:

Abbott agrees to comply with this request.

- **Please also conduct subgroup analyses for all efficacy endpoints, in all requested analyses, according to “low” vs. “high” total daily levodopa dose at the end of the trials when diary data were collected (a new request). Please show respective results for each endpoint on the same page for “low” and “high” LD for each treatment (LCIG vs. oral LD/CD). There should be 4 columns of results on each page (2 columns for each treatment). The DNP will provide the cut-off/threshold for distinguishing “low” from “high” dose LD in the final meeting minutes.**

Sponsor Pre-Meeting Response FDA Preliminary Comment:

The Sponsor is concerned about multiplicity issues that may arise given that there are 46 efficacy variables. Abbott proposes that we perform those analyses on normalized and absolute diary variables, but not on percent change variables or on other efficacy variables not obtained from PD symptom diaries. We propose conducting this analysis using the total of all sources of levodopa including study drug, and all uses of Sinemet IR tablets, as described in the response provided 05 Aug 2012.

Does the Agency agree with these proposals?

In response to our request, you submitted an individual patient listing of daily total levodopa doses for all patients during the last treatment week (week 12) in your pivotal trials. Although diary data were supposed to be collected on 3 days, this listing

shows levodopa results ranging from 1 day to 19 days for each patient. Furthermore, the protocol specified that the levodopa (for LCIG or oral LD/CD) dose remain constant during the maintenance period (including week 12). It is readily apparent that there were some patients with significant changes in the total levodopa daily dose during this last week of treatment. In particular, there were many instances in which the total levodopa dose was significantly lower than other doses for 1 or 2 days during the last 3 days of the trial (potentially when diary data were collected for the primary efficacy endpoint) for the oral LD/CD treatment group. There were also a few instances in which the total levodopa dose was significantly higher than other doses on 1 or 2 of the last 3 days of the trial for LCIG treated patients. If diary data were collected on days where significant changes in the total levodopa daily dose were made, these changes might favor a better therapeutic response for LCIG compared to oral LD/CD. Please explain:

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

The Abbott responses sent 05 Aug 2012 address these questions. We will ensure that this information is clearly presented in the NDA.

- 1) why there are such large differences in the data (i.e., 1-19 days of data) presented for individual patients over supposedly only the last 7 days (week 12) of the trials?

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

The Sponsor acknowledges the Agency's comments and will ensure that this data is presented fully and clearly in the NDA.

- 2) why there were some patients that had large differences in the total daily levodopa dose at a time when the protocol specified that the dose remain unchanged?

Sponsor Pre-Meeting Response to FDA Preliminary Comment:

The Sponsor acknowledges the Agency's comments and will ensure that this data is presented fully and clearly in the NDA.

Meeting Discussion:

- *In response to sponsor's question with regard to variables in analysis datasets, the Agency requested that in addition to having average time of "off", "on" and "on without troublesome dyskinesia", the primary dataset should include daily time for Days 1, 2 and 3 as well as number of valid hours on Days 1, 2 and 3. The data at all visits need to be included. In addition, main demographic variables (age, gender and race) and region information need to be included in the primary dataset.*
- *The Agency reiterated their request that the sponsor submit all requested efficacy analyses in all combinations (e.g., for various efficacy endpoints with various populations and with various analytical approaches). The Agency's recent*

Preliminary Responses outlined what appeared to be deficiencies in the Sponsor's plan compared to what the Agency had requested in November 2011. The Sponsor informed the Agency that one of its requested analyses "non-resistant" patients would not be conducted because there were too few patients in that category.

- *The Agency recommends that the sponsor submit a listing of all the planned efficacy analyses with the title of each analysis to help ensure that the sponsor is planning to conduct the additional analyses of interest to the Agency's reviewers before submitting the NDA. The sponsor acknowledged and agreed to this request.*
- *The Agency will make recommendations regarding the format of some efficacy analyses in the final meeting minutes along with its comments and recommendations for the safety analyses.*
- *The Agency recommends that the sponsor submit an individual patient listing (for the controlled trials) that specifies the total daily levodopa dose for each patient during the last treatment week. This listing should also include other relevant patient demographic treatment information including*
 - *Patient ID*
 - *Age*
 - *Gender*
 - *Treatment assignment*
 - *Total daily LD dose at baseline*
 - *Average total, daily levodopa dose for maintenance phase of trial (weeks 5-12), total*
 - *Total daily levodopa dose for each day during the last week of treatment and specification of which days efficacy diary data were collected*
 - *Average total, daily levodopa dose on days efficacy diary data were collected*
- *The clinical reviewer noted that it had not seen the sponsor's most recent response to questions posed about the levodopa dosing data for the last week (week 12) of the controlled trials.*

Post-Meeting Comment:

- *The Agency remains interested in the "high" and "low" dose analyses for all the efficacy analyses as requested in an earlier meeting. The DNP recommends that "high" dose total, daily levodopa be defined as 1250 mg levodopa or higher and that "low" dose total, daily levodopa be defined as less than 1250 mg.*

- *The DNP had recommended conducting analyses for “low” and “high” total daily levodopa dose for the efficacy analyses requested and to present these results in four columns including two columns for “low” and “high” dose for each treatment (LCIG vs oral LD/CD. The DNP would like to revise its request to present all the efficacy analyses in landscape format in 6 columns (three columns – “any” dose, “low dose,” “high” dose for each treatment LCIG vs oral LD/CD) **on the same page**. In such a presentation, results for all efficacy endpoints could easily be compared simultaneously relative to dose **within a treatment and across a treatment**. This format for presentation has also been outlined in the Appendix for all DNP requested/recommended safety analyses.*

Question 14:

Does the Agency agree with this proposal?

Preliminary FDA Response:

Yes

Meeting Discussion:

No further discussion at the meeting.

Question 15:

On the basis of the clinical data and Regulatory rationale provided, does the Agency agree that the proposed LCIG NDA submission qualifies for Priority Review? If not, are there other factors that the Agency would consider when determining Priority Review status?

Preliminary FDA Response:

The Agency does not agree that your NDA qualifies for priority review status. (b) (4)

Priority Review status requires demonstration of a clinically meaningful improvement over available therapy (including nondrug therapy). The decision to combine the two pivotal trials into a single trial no longer left an opportunity to demonstrate replication of efficacy in two adequate and well controlled clinical trials.

Meeting Discussion:

No further discussion at the meeting.

Question 16:

Does the Agency agree with the timing of the safety update submission?

Preliminary FDA Response:

Yes

Sponsor Pre-Meeting Response to our Preliminary Comment:

The Sponsor would like to clarify that if the NDA is not subject to a priority review then we intend to submit the safety update at Day 120.

Meeting Discussion:

No further discussion at the meeting.

Question 17:

Abbott believes that the testing performed allows adequate evidence for description of the demand dose feature in the USPI and does not plan to submit further data, other than those described above, in the NDA. Does the Agency agree that no further data are required to describe the demand dose feature in the USPI?

Preliminary FDA Response:

It is premature to agree that no information related to demand dosing will not need to be included in the package insert. The information related to performance of the demand dose function should include device performance and human factors testing to validate that intended users are capable of safely and effectively using the demand function (and the device) to deliver the drug.

Meeting Discussion:

Information regarding the demand dose function is required to support labeling information for this function.

Question 18:

Does the Agency agree that a request for a full waiver for pediatric studies in the upcoming NDA submission would be granted?

Preliminary FDA Response:

Typically, PeRC grants waivers from PREA requirements for pediatric studies for drugs intended to treat Parkinson's disease. You must still include a request for a PREA waiver with a justification in the application.

Meeting Discussion:

No further discussion at the meeting.

Question 19:

Would the Agency provide guidance as to whether the LCIG System will be subject to review by an Advisory Committee?

Preliminary FDA Response:

We will need to complete substantial review (generally, by the filing deadline) of the application before deciding if an Advisory Committee will be convened.

Meeting Discussion:

The Agency not anticipate convening an Advisory Committee for the LCIG NDA, however, the final decision requires the Agency begin substantial review of the NDA.

Question 20:

Does the Agency agree with this plan?

Preliminary FDA Response:

We request that you provide analyses of safety data from non-IND trials using similar methods and format as those used for the trials conducted under the IND. Present individual non-IND trial results, the combined results from all of the non-IND trials and integrate them into the ISS.

Sponsor Pre-Meeting Response to our Preliminary Comment:

The Sponsor would like to further discuss the appropriateness of integrating the safety data from the non-IND studies into the ISS.

Objectives of the Non-IND Programs

Program number/name	Objective	Report in NOA
Retrospective Chart Reviews		
S127.4.005 - Finland	Retrospective review of patient charts to collect Finnish health care resource use	Yes
S127.4.007 - Survival Sweden	A retrospective review of charts of patients treated with Duodopa in Sweden between January 1991 and June 2008.	Yes
Registry, Program 1 (voluntary Data Collection) and HEOR Studies		
S127.4.001 - DAPHNE Sweden	Long-term data collection for HEOR outcomes with Duodopa in Advanced PD: Health outcomes and net economic impact	Yes
S127.4.006 - RELEVANT - EU	Long-term voluntary data collection registry program of treatment changes for patients treated with Duodopa, Standard of Care Oral Treatment, Apomorphine or DBS	Yes
S127.4.002 - Belgium	Long-term voluntary data collection of safety and effectiveness of Duodopa. Requested by the Belgian National Social Health Institute (INAMI) to support reimbursement.	Yes
S127.4.004 - GLORIA - EU	Long-term voluntary data collection registry program on efficacy and safety of Duodopa in patients with advanced PD in routine care	Ongoing - Interim to be provided
Phase 3 Studies		
M12-925 - Japan	Phase 3, short-term, NJ phase treatment of LGS in advanced PD patients (n=8)	Ongoing - will be summarized

Pre-Clinical Safety Data
TEAE/SAE/TEAE
12/1/12

Company Confidential
S127-0001



The rationale for not integrating the Non-IND programs with the Phase 3 safety data include the following:

- Six of the seven studies described were not interventional clinical studies. They included 2 retrospective chart reviews, 1 Health Economic Outcome Research (HEOR) study and 3 voluntary data reporting registries.
- With the exception of 4001 (HEOR study) and M12-925, data that have been generated more closely resemble spontaneous post-marketing reporting as opposed to controlled clinical studies. Data reporting was voluntary and monitoring was limited
- Incomplete safety profiles were collected. Unlike IND studies only serious suspect (associated) adverse reactions were collected.
- None of the above studies can be validly compiled into an ISS data presentation, or analyzed in a manner similar to the IND studies.

None of the data derived from these studies alters the safety or risk-benefit profile of the product, as defined by the clinical development program.

In order to facilitate review of this data we intend to:

- Summarize the data individually by study in the ISS
- Submit each of the study reports
- Summarize in a single table TEAE, Related, Severe, SAE, TESAE, Pre-term, Pre-Term TEAE, Deaths

Does the Agency agree with our proposal?

Meeting Discussion:

The Agency accepts Abbott's proposal for submission of the non-IND trial information.

Question 21:

Does the Agency agree with the proposed time period for safety data to be included in the safety update?

Preliminary FDA Response:

Yes, however, handle updated safety information for non-IND trials in the same way as the information from trials performed under the IND.

Meeting Discussion:

No further discussion at the meeting.

Question 22:

Does the Agency have any comments on the ISS SAP?

Preliminary FDA Response:

Yes. We have additional comments and recommendations regarding the ISS SAP. We will provide our additional comments and recommendations regarding the content and format of information/data/analyses in the ISS SAP in an appendix with the final meeting minutes.

Sponsor Pre-Meeting Response to our Preliminary Comment:

Abbott would like to discuss the timing of the responses.

Meeting Discussion:

The Agency noted that its comments/recommendations would be sent in advance of the Agency's meeting minutes if possible, however it was more likely that the comments would be sent with the final meeting minutes.

Additional Clinical Pharmacology Comments

1. Please clarify whether the tube implanted into the upper jejunum by percutaneous endoscopic gastrostomy is only for LCIG administration. If this tube is also used for the other drug administration and/or food taken, please provide justification on how to avoid the potential compatibility/interaction issues.

Sponsor Pre-Meeting Response to our Preliminary Comment:

The Sponsor would like to clarify that the PEG- J tube is used for LCIG administration only.

2. You have reported that, for hydrazine, plasma concentrations at steady-state in the majority of evaluated subjects on LCIG treatment (10 of 11) were not measurable. To assure that the methodology used to measure hydrazine is validated and sensitive enough, please provide the assay report as well as the raw datasets in the NDA submission.

SUBMISSION OF POPULATION PK DATA

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table should be submitted which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. Also provide in the summary of the report a description of the clinical application of modeling results.

Sponsor Pre-Meeting Response to our Preliminary Comment:

The Sponsor acknowledges the additional clinical pharmacology comments and agrees to the recommendations.

Meeting Discussion:

No further discussion at the meeting

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS
Appendix.

APPENDIX

DNP RECOMMENDATIONS FOR ISS ANALYSIS PLAN (ISAP)

General

- For the randomized, double-blinded, controlled trials (combined S187.3.001/S187.3.002), ideally, it is most desirable for analytical comparisons to present all safety results for all analyses on the same page according to treatment (LCIG vs placebo for all patients (i.e., any LD dose) in each treatment group and also according to total daily levodopa dose such as “high dose” (HD) vs “low dose” (LD) of total, daily levodopa dose. Specifically, please present all safety results/analyses (in landscape format) for LCIG-treated patients in three columns (one for all patients regardless of levodopa dose; one for the subgroup of LD; one for the subgroup of HD) and results for oral LD/CD-treated patients similarly. “High” dose is defined as a total, daily levodopa dose of 1250 mg or higher and “low” dose is defined as a total, daily levodopa dose that is less than 1250.

Please present all open-label, extension safety data for all 3 trials for according to three dosing categories (i.e., “any,” LD, and HD total, daily levodopa dose) on the same page only for the integrated pooled analyses. It is not necessary to present the separate analyses for each of these three trials according to dose. For the categorization of patients in the open-label, long-term exposure analysis set according to LD or HD, please compute the mean total, daily levodopa dose over the whole trial.

- Please also conduct all safety analyses according to various subgroups of patients :
 - regional subgroups (3) as patients from 1) North America; 2) Western Europe, Oceania Countries, and Israel combined; 3) Asian, and Eastern European Countries combined
 - males vs females
 - patients ≥ 65 years old vs < 65 years old
 - presence or absence of concomitant treatment with at least one dopaminergic agonist)

All these subgroup analyses should be presented according to treatment for controlled trial data and for all patients for open-label trial data. To facilitate comparisons, present all open label trial analyses for all patients, and for each subgroup on the same page in 3 columns. To facilitate comparisons of results of controlled trial data, present results for each subgroup under each treatment on the same page in 4 columns (i.e., 2 subgroups under each treatment with the exception of the regional subgroup analyses that will include 3 subgroups under each treatment).

You have proposed subgroup analyses for the open-label, long-term exposure analysis set according to 5 regions. We are particularly interested in you presenting

these safety data according to 3 regions (i.e., North America vs Western Europe, Oceania Countries and Israel combined, vs Asian, and Eastern European Countries combined). Although we do not object to analyzing and presenting results for 5 regions, we do not consider it necessary to analyze the 5 regions separately.

You can decide if it is appropriate to conduct subgroup analyses based upon race after reviewing the number of patients from difference races.

- Please present cumulative dose-duration exposure tables based upon mean total daily levodopa dose for the whole exposure and show exposure for “any” dose, LD, and HD for any treatment time, ≥ 6 , ≥ 12 , ≥ 18 , and ≥ 24 months treatment. In cumulative exposure tables, patients treated for longer periods are also included in exposure results for shorter periods. You are welcome to show results for treatment periods longer than 24 months if such data are available. You can combine controlled and open-label treatment in these dose-duration exposure tables.
- Present all analyses (central tendency and outliers) for each safety parameter (e.g., vital signs, clinical laboratory analytes, ECG parameters) over time (showing baseline and results from all post baseline visits until the end of the trial). Central tendency analyses should include mean data and other descriptive parameters. Outlier analyses should show the numerator relative to denominator and respective %.
- Present results for incidence for all outlier analyses (for orthostatic VS, clinical laboratory analytes, ECG parameters) according to time perspective of “any” visit and also at “final” visit.
- Present all central tendency analyses for the mean absolute result and for the mean change from baseline for each safety parameter (i.e., orthostatic vital signs, clinical laboratory analytes, ECG parameters).
- Please interpret and discuss all analyses presented in the ISS within the ISS. Whenever there is a need to refer to any data within the ISS or “outside” of the ISS, hyperlinks to these data should be provided.
- Please include a detailed Table of Contents (TOC) for the ISS with a list of all tables, figures, and listings and ensure the ability to hyperlink to any page shown in the TOC. Please do the same for every report and document in the NDA.
- It is not necessary to conduct statistical analyses for safety data. Although it is all right for you to do so. We do not expect statistical analyses for safety data. Instead, we expect descriptive analyses. Because safety outcomes are not powered to show statistical significant, the lack of statistical significance (i.e., $p < 0.05$) for any safety outcome does not indicate that there is no basis for a safety concern.

- We recommend that you submit shells of the planned safety analyses (including all Agency recommended analyses) for review and feedback after reviewing the Agency recommendations. Because many of these analyses will follow the same format, it is not necessary that a shell be presented for each safety analysis when the format is identical. Prototypical shells of all these data can be submitted for review and feedback. Once you have determined the specific format for individual trial and integrated/pooled analyses, we recommend that you submit a list (with descriptive names of all tables) of individual safety analyses planned (including all Agency recommended analyses), that would follow specific formats, for DNP review and feedback. Submission of this list for our review will help ensure that you are planning to submit all the safety analyses that we want and that we have requested.

- Please ensure that the ISS is electronically constructed accurately/correctly to show appropriate page coordination in every respect/situation. For example, the page number shown in the table of contents should be the same page number shown on the page after one hyperlinks to that page and when a print command is given to print that page.

- We recommend that you review the following guidances for assistance in planning your NDA submission in general but in particular for planning the details about the format and content of your ISS:
 - Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
 - Guidance for Industry M4: The CTD — Efficacy Questions and Answers
 - Format and Content of Clinical and Statistical Sections of Application
 - Format and Content of the Summary for New Drug and Antibiotic Applications
 - Formatting, Assembling and Submitting New Drug and Antibiotic Applications
 - Regulatory Submissions in Electronic Format; General Considerations

You can contact the division for advice if unusual questions arise as to the content and format of your submission and the answers are not contained in any of these guidances.

Adverse Events

- Please provide summary tables for all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs causing study discontinuation from a time perspective and from a dose-perspective (as previously outlined) for the controlled trial data. All of these TEAE data should be presented for :
 - 1) the whole trial period for any TEAE with onset at any time in the whole trial;
 - 2) titration/dose adjustment period (i.e., initial 4 weeks of double-blinded treatment, weeks 1-4) for any TEAE with onset in this period;

- 3) maintenance period (weeks 5-12 when levodopa treatment (for LCIG or oral LD/CD is supposed to be stable) for any TEAE with onset in this period; and
- 4) “persistent” TEAEs from the titration period into the maintenance period for a certain period of time (we recommend ≥ 7 days for this definition of “persistent”).

Analyses of TEAEs according to a time perspective can be very helpful in characterizing the risks of certain TEAEs at particular times relative to treatment. Such information can also be important for inclusion in the label.

- Please present all these types of TEAE summary tables for each open-label extension trial according to the aforementioned time perspective.
- Please present all these types of TEAE summary tables for the pooled open-label extension trials according to the aforementioned time perspective and dose perspective (i.e., any dose, LD, and HD for total daily levodopa dose).
- Please provide a definition of TEAE including the time after the last treatment dosing for considering that an adverse experience is a TEAE.
- Please present all 3 categories of narrative summaries (i.e., SAEs, discontinuations for TEAEs, TEAEs of special interest) associated with LCIG treatment in a single location in the ISS. Within each of the 3 categories, present narratives according to study. Please construct each narrative summary chronologically with the aim of making each summary as comprehensible as possible. In the past, it has been difficult to comprehend what actually happened with the typical narrative summary for LCIG reported to the Agency. To facilitate better construction of narrative summaries for maximal comprehension of each narrative summary, we recommend that you note :
 1. dates of onset and resolution (or days after starting investigational treatment) for onset of signs/symptoms of the TEAE and their resolution;
 2. pertinent positives and negatives for the TEAE prompting the narrative;
 3. starting and stopping dates of concomitant medications and doses;
 4. supportive medical data (e.g., results of X rays or other imaging, laboratory tests and notation if abnormal, ECGs etc.); and 5) the chronological course of each patient including outcome.

Please also provide a comprehensive listing of all patients and adverse events prompting a narrative summary at the beginning of the section containing narratives and specify the page location of each subject’s narrative and provide a hyperlink to the narrative. Please hyperlink the term(s) describing the TEAE in the comprehensive list of all narratives to the specific section of the narrative dealing with that specific TEAE. This specific request is made because some chronological narratives can be quite long and complicated and include many paragraphs describing many TEAEs prompting a narrative over 2 or more pages. Hyperlink all references (within a study

report) to a specific patient experiencing a TEAE requiring a narrative to the specific narrative located in the ISS section.

This listing should outline the following information:

- patient ID #
 - age
 - gender
 - specific TEAE
 - type/category of TEAE prompting a narrative summary
 - outcome
- Because we recommend MedDRA coding for adverse events, we are pleased to note that you plan to code according to a MedDRA medical dictionary. Please specify the version of MedRA used and use the same version for all coding.
 - Include the adverse event coding dictionary as a PDF file and show how investigator verbatim terms were mapped to preferred terms and also how preferred terms are mapped to investigator verbatim terms.
 - If you present any analyses according to investigator assessment of causality, we recommend that you use a binary categorization as “unlikely” (e.g., combining “unrelated” and “unlikely,” and combining “possible” and probable”).
 - We recommend “worst case” analyses that show the incidence of adverse events possibly suggestive of hypotension/orthostatic hypotension and also possibly suggestive of falls for the controlled trials according to treatment and the time and dose perspectives outlined previously. For conducting such analyses, we recommend that you determine a case definition based upon a variety of adverse event terms (i.e., both preferred terms and investigator verbatim terms) that could possibly suggest the occurrence of hypotension/orthostatic hypotension or a fall. If a patient experiences any one or more of the various adverse event terms defining the case definition of hypotension/orthostatic hypotension or a fall, the incidence of that adverse event phenomenon is determined.

For adverse events possibly suggestive of a fall, we recommend that you consider the following terms that might be included in this search including: fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the event was not a result of a fall. The DNP is recommending this minimal list of adverse event terms of how one might analyze for “falls” adverse event terms (e.g. some examples but this is not necessarily a complete list). You can add additional terms to the case definition if you think that they are appropriate/relevant.

For adverse events possibly suggestive of hypotension/orthostatic hypotension, we recommend that you consider including the following terms in this search: blood

pressure orthostatic decreased, dizziness postural, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension, dizziness, vertigo, lightheadedness, postural lightheadedness, impaired balance, and feeling drunk. You should consider such events possibly suggestive of a hypotension/orthostatic hypotension unless there is information to suggest that the event was not a result of hypotension/orthostatic hypotension. The DNP is recommending this minimal list of adverse event terms of how one might analyze for hypotension/orthostatic hypotension adverse event terms (e.g. some examples but this is not necessarily a complete list). You can add additional terms to the case definition if you think that they are appropriate/relevant.

Please conduct these analyses for the incidence of adverse events possibly suggestive of falls and of hypotension/orthostatic hypotension for any TEAE, SAEs, TEAEs causing study discontinuation from a time perspective and also dose perspective.

Clinical Laboratory Analytes

- Present all outlier analyses for clinical laboratory results showing abnormal results according to whether the result is “low” or “high” based upon whether the result is outside of the “normal” reference range for each laboratory analyte.
- Present all outlier analyses for markedly abnormal clinical laboratory analytes (i.e., markedly decreased/low and markedly increased/high) according to the threshold for markedly abnormally high and low.
- For the controlled trials and for each of the open-label extension trials, please submit for review and feedback a table showing the normal reference range for every clinical laboratory analyte, your proposed threshold for a markedly abnormally decreased and increased threshold value, and additional columns for DNP recommendations/comments. Please also let the Division know whether you recommend the same threshold criteria for markedly abnormally low and high for the three extension trials or a different threshold for each trial. We will review these tables and provide feedback/comments/recommendations.

Vital Signs

- We recommend presenting analyses of central tendency and outliers over time (at every trial visit from baseline until the final trial visit) for orthostatic vital signs (VS). Present systolic BP, diastolic BP and pulse relative to position (i.e., supine, standing, or change from supine to standing) over the whole controlled trial period (including the intensive VS monitoring on days 1, 8, and 43) and over treatment under open-label conditions. In these orthostatic analyses, the supine VS result should be subtracted from the standing VS result (i.e., standing VS result – supine VS result).

- For all post-treatment/randomization VS that are not measured during the intensive data collection post dosing on days 1, 8, and 43, please compare changes from baseline to the mean of the replicate measurements of VS at baseline/pre-treatment collected at the beginning of the trial (e.g., controlled trials and open-label trials respectively). For all post-dosing VS measured during the intensive data collection on days 1, 8, and 43, please compare post-dosing changes to the mean of the replicate measurements of VS at the pre-dosing time period for controlled trials and open-label trials respectively.
- We recommend applying various outlier criteria for orthostatic VS for systolic and diastolic blood pressure and pulse. We are working on completing shells describing and outlining the content and format that the DNP recommends for presenting results of outlier and central tendency analyses. Upon their completion (that is expected within a week), these shells will be provided to you.
- We recommend that you analyze all data for vital sign (VS) outliers according to:
 1. the VS criteria recommended by the DNP (and provided in the tabular shells for presenting VS analyses);
 2. the criteria that you have proposed in Table 4 for Statistical Analysis Plan for the ISS; and
 3. also all to the criteria in Table 4 applied separately not only in combination as shown for “low” and “high” criteria for SBP, DBP, and pulse. For example, you have proposed “low” criteria for SBP by requiring a value of ≤ 90 and > 30 decrease from Baseline).

Because combined criteria can be very insensitive for detecting significant or noteworthy outliers, we request that you also conduct outlier analyses for a value of < 90 applied alone, and for a decrease of > 30 from Baseline applied alone, in addition to the combined criteria that you have proposed. Please also analyze all of the other combined criteria separately for SBP, DBP, and pulse.

ECGs

- Please conduct analyses of ECG parameters for central tendency and outliers over time similarly as requested for VS in the open-label and controlled trial experience (including the intensive ECG data collection on days 1, 8, and 43).
- Please present the content and format of ECG data similarly as recommended for presenting results for VS in the tabular shells provided by the DNP.
- Please provide outlier analyses for these key ECG parameters of interest including :

- QTc (for Bazett and Fridericia correction for all QTc analyses) of ≥ 500 , ≥ 480 , and ≥ 450 msec at any time post-baseline/randomization/treatment time
- QTc change from baseline or change from pre-dosing at ≥ 30 msec, and ≥ 60 msec

Post-Marketing Experience

- Please provide a comprehensive integrative review of the post-marketing safety experience globally for LCIG. Please also pay particular attention to the list of TEAEs of special interest.

Published Literature

- Please provide a comprehensive integrative review of the published literature for LCIG. Please also pay particular attention to the list of TEAEs of special interest. Please provide copies of all publications referenced as well as hyperlinks to every publication referenced/discussed in the ISS.

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

/s/

ERIC P BASTINGS
09/07/2012
Signed for Dr. Katz



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

January 18, 2000

Nouvel Pharma, Inc.
11322 Acuff Lane
Lexa, KS 66215

Attention: Daniel E. Walker, PhD
President and CEO

Dear Dr. Walker:

Reference is made to your orphan drug application of submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of levodopa/carbidopa as an orphan drug (application #99-1294).

We have completed the review of this application and have determined that levodopa/carbidopa qualifies for orphan designation for the treatment of late stage Parkinson's disease. Please note that it is levodopa/carbidopa and not its formulation that has received orphan designation.

Please be advised that if levodopa/carbidopa were approved for an indication broader than the orphan designation, your drug might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA. Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of levodopa/carbidopa as designated. Also an annual progress report must be submitted

within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Donald R. Haggerty, MD, MPH at (301) 827-0986.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

A handwritten signature in cursive script, reading "Marlene E. Haffner".

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development