

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206321Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206321

SUPPL #

HFD # 510

Trade Name Saxenda

Generic Name liraglutide injection, 3 mg

Applicant Name Novo Nordisk

Approval Date, If Known 12/23/14

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)(1)

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

Did not request specific # of 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?

N/A

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).

NDA# 022341

Victoza

NDA#

NDA#

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#

NDA#

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:

1. Trial 1839: Obese and overweight subjects with comorbidities
2. Trial 1922; Obese and overweight subjects with T2DM

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 YES NO

Investigation #2 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 YES NO

Investigation #2 YES NO

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

N/A

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"):

1. Trial 1839: Obese and overweight subjects with comorbidities
2. Trial 1922; Obese and overweight subjects with T2DM

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
IND # 73206 YES !
! NO
! Explain:

Investigation #2
IND # 73206 YES !
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1 !
! YES ! NO
Explain: ! Explain:

Investigation #2 !
! YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Patricia Madara
Title: Regulatory Project Manager
Date: 12/23/14

Name of Office/Division Director signing form: James P. Smith
Title: Deputy Director (acting), DMEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

PATRICIA J MADARA
12/23/2014

JAMES P SMITH
12/23/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 206321 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: Saxenda Established/Proper Name: liraglutide [rDNA origin] Dosage Form: injection		Applicant: Novo Nordisk Agent for Applicant (if applicable):
RPM: Patricia Madara		Division: DMEP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check:</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>10/20/14</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 checked="" type="checkbox"/> None
❖ 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 _____	<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, (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):
(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 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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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 type="checkbox"/> None <input checked="" 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)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ 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	
❖ 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
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date AP: 12/23/14
Labeling	
❖ 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-see AP letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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 <input checked="" type="checkbox"/> Device Labeling (containers) <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- see AP letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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 – see AP letter
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	Letter: 4/3/14 Review: 4/1/14
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 7/22/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 10/15/14 OPDP: <input type="checkbox"/> None 8/14/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews <i>(e.g., RPM Filing Review⁴/Memo of Filing Meeting)</i> <i>(indicate date of each review)</i>	3/28/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 12/23/14
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/8/14</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	included
❖ 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)	included
❖ 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>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 9/10/2013 <input type="checkbox"/> No mtg 3/10/2008 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input type="checkbox"/> No AC meeting 9/11/14
Decisional and Summary Memos	
❖ 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 11/10/14 (acting deputy director)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None same as above
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 9 templates 12/23/14
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review see acting deputy director review 10/18/14; 2/26/14 <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>)	Clinical review Clinical review, page 28
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DNP 10/21/14; SEALD 10/3/14; MTC 9/26/14; drug use 8/5/14; DEPI 8/18/14, 7/25, 6/30; DPV 8/13/14; DOP I 7/3/14;

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ 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>) 	Final submission – 12/17/14 – see approval letter; earlier versions: 12/12/14, 11/18/14; 11/10/14; 10/2/14; 8/20/14; 12/20/13; REMS memo 12/22/14 <input type="checkbox"/> None DRISK 12/11/14; 11/14/14; 11/7/14; 10/16/14; 9/26/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested Summary review: 9/2/14; Letters included
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	
❖ 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 DB VII 9/12 and 2/18 /14; DB II 10/16, 9/15 and 2/20/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ 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 9/19/14 and 2/26/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ 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 checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/15, 9/3 and 2/5/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None DB VI 6/19/14
❖ 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 Reference Victoza
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ 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 biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/21/14 (memo); 5/14/14 and 1/23/14
❖ Microbiology Reviews <input checked="" 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 1/16/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	Review 5/14/14: pages 28-29
<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>	
❖ 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: 10/20/14 <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 type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input 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 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 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 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 type="checkbox"/> Done

From: Guettier, Jean-Marc

Sent: Monday, December 22, 2014 5:07 PM

To: 'RBCL (Bob Clark)'

Subject: RE: Saxenda NDA 205321

Importance: High

Mr. Clark,

Thank you for your email below. We have also received your letter of December 17, 2014 from Robert Clark to Jean-Marc Guettier, M.D., Director, CDER DMEP.

Based on these communications, the Agency understands that Novo Nordisk A/S and Novo Nordisk Inc. agree to make certain commitments, including the five commitments stated in our letter to you of December 16, 2014. These are copied here for reference:

1. A commitment to comply with the REMS for Victoza, NDA 22314
2. A commitment to comply with the REMS for Saxenda, NDA 206321 (if approved)
3. A commitment to monitor and audit your compliance with the requirements of the Victoza REMS, and to report the results of those monitoring and auditing activities to FDA
4. A commitment to ensure that adequate processes are in place to ensure compliance with the requirements of the Saxenda REMS (if approved), and to provide documentation of those processes and procedures to FDA
5. A commitment to monitor and evaluate implementation of the Saxenda REMS, and report results of these evaluations to FDA

Please notify us by noon on December 23, 2014, if Novo Nordisk A/S and Novo Nordisk Inc. are not fully committed to any of the above.

As noted in our letter to you of December 16, 2014, FDA intends to conduct regular evaluations of your compliance with the Victoza REMS and the Saxenda REMS (if approved). FDA may require assessments beyond those required by the REMS, as provided for in the timetable for assessments, if we determine these further assessments are needed.

Best Regards,

Jean-Marc Guettier, MDCM

Division Director
Division of Metabolism and Endocrinology Products
US Food and Drug Administration

-----Original Message-----

From: RBCL (Bob Clark) [mailto:rbcl@novonordisk.com]
Sent: Thursday, December 18, 2014 4:25 PM
To: Guettier, Jean-Marc
Subject: Saxenda NDA 205321

Dr Guettier: Novo Nordisk responded yesterday to the FDA letter signed by Dr Woodcock related to the NDA listed above. In our response we picked up the exact language used in FDA's letter for points 1,2 and 4. For point 3 we wanted to propose [REDACTED] (b) (4). For point 5 we are proposing [REDACTED] (b) (4).

I tried to clarify these two points in my letter yesterday to ensure that we were meeting FDA's expectations. We do agree with and commit to undertake the 5 points in the FDA letter from Dr Woodcock but we wanted to be clear as to our interpretation of the request.

If there are any questions please feel free to contact me.

Best regards,

Bob

Robert Clark

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/s/

JULIE C VAN DER WAAG

12/22/2014

J.Van der Waag entering email correspondence into electronic archive on behalf of Dr. Guettier



NDA 22341
NDA 206321

INFORMATION REQUEST

Novo Nordisk Inc.

Attention: Lars Rebien Sorensen, CEO
Robert Clark, VP, U.S. Regulatory Affairs
Mads Krogsgaard Thomsen, Executive VP & CSO

P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Sorensen, Mr. Clark, and Mr. Thomsen:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide [rDNA origin] injection) and Saxenda (liraglutide [rDNA origin] injection).

Thank you for your participation in our teleconference on November 7, 2014, (FDA participants included Dr. Janet Woodcock, Director, CDER; Dr. John Jenkins, Director, CDER OND; Grail Sipes, Director, CDER ORP; and Julie Van der Waag, CDER CPMS, DMEP). We have also received your submission dated November 18, 2014, submitted as an amendment to NDA 206321 for Saxenda.

Based on our teleconference on November 7, 2014, and your November 18, 2014, submission, the Agency understands that Novo Nordisk A/S and Novo Nordisk Inc. have made a number of commitments, including the following:

1. A commitment to comply with the REMS for Victoza, NDA 22314
2. A commitment to comply with the REMS for Saxenda, NDA 206321 (if approved)
3. A commitment to monitor and audit your compliance with the requirements of the Victoza REMS, and to report the results of those monitoring and auditing activities to FDA
4. A commitment to ensure that adequate processes are in place to ensure compliance with the requirements of the Saxenda REMS (if approved), and to provide documentation of those processes and procedures to FDA
5. A commitment to monitor and evaluate implementation of the Saxenda REMS, and report results of these evaluations to FDA

Please notify us within 48 hours of your receipt of this letter if Novo Nordisk A/S and Novo Nordisk Inc. are not fully committed to any of the above.

FDA intends to conduct regular evaluations of your compliance with the Victoza REMS and the Saxenda REMS (if approved). FDA may require assessments beyond those required by the REMS, as provided for in the timetable for assessments, if we determine these further assessments are needed.

We also ask that you submit your November 18, 2014, communication to NDA 22341 for Victoza.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JANET WOODCOCK
12/16/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) REMS revisions requested
Date: Thursday, December 11, 2014 5:03:00 PM
Attachments: [FDA to NN_11Dec14_proposed-rems-cleanFDA_Revised.doc](#)
[FDA to NN_11Dec14_proposed-rems-support-cleanFDA_Revised.doc](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application. Please see the comments below. We are requesting revisions to the REMS factsheet.

1. FDA determined there is a need for clarification of the requirement for a REMS Factsheet as part of the communication plan included in the Saxenda REMS. FDA requests that you revise the Saxenda REMS Document as follows:

Communication Plan, section 2) REMS Factsheet: "A REMS Factsheet will be made available to healthcare providers and distributed through Novo Nordisk SAXENDA[®] field based sales or medical representatives during the initial healthcare provider discussion within the first 18 months after approval of this REMS. (b)
(4)

[REDACTED] [Novo Nordisk SAXENDA[®] field based sales or medical representatives will verbally review each risk message contained in the Factsheet.](#)"

2. Resubmit the revised version of the REMS document and REMS Supporting Document. The REMS Supporting Document must reflect the changes made to the REMS document. The next submission must include:
 - a. final clean versions (MS Word and PDF) of all REMS-related materials (i.e. REMS appended materials and REMS Supporting Document), and
 - b. redline version of the REMS Document and REMS Supporting Document must be also included in this submission to facilitate FDA's review of the implementation of the changes requested.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
12/11/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 7, 2014

**Application Numbers/
Product Names:** NDA 22341 Victoza (liraglutide [rDNA origin] injection)
NDA 206321 Saxenda (liraglutide [rDNA origin] injection)

Sponsor/Applicant Name: Novo Nordisk Inc.

Subject: Risk Evaluation and Mitigation Strategies (REMS)

FDA Participants

Janet Woodcock	Director, CDER
John Jenkins	Director, OND
Grail Sipes	Director, ORP
Julie Van der Waag	CPMS, DMEP

Novo Nordisk Participants

Lars Rebien Sorensen	CEO
Bob Clark	VP, U.S. Regulatory Affairs
Mads Krogsgaard Thomsen	Executive VP & CSO

Discussion

Dr. Woodcock stated that CDER had recently been made aware of evidence that Novo Nordisk has failed to comply with the REMS for Victoza, specifically regarding the requirement that the sponsor inform healthcare providers about the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis). CDER is very concerned about the prospect of approving a new product (Saxenda) with the same active ingredient, at a higher dose, given the evidence that Novo Nordisk has engaged in behavior related to the Victoza REMS that appears to have been designed to undermine the risk message.

(b) (7)(A)

1 Page(s) has been Withheld in Full as b7A immediately following this page

FDA asked for the personal commitment of the Novo Nordisk CEO that the pattern and practice of violating the Victoza REMS will be stopped and that the company will comply with the REMS for Saxenda, if approved. The CEO verbally committed to comply with the REMS. Novo Nordisk also verbally committed to:

1. Perform an audit of current practices with regard to the Victoza REMS and then report to FDA the results of their investigation. FDA suggested that this investigation should also examine why the company was unable to uncover the REMS violations despite the oversight and management systems the sponsor said were in place.
2. Develop a plan to ensure that REMS requirements will not be undermined in the future, and provide substantiation to FDA of policies and procedures that will support that commitment.

Novo Nordisk will submit this commitment in writing to the relevant NDA, in a letter to be signed by Lars Rebien Sorensen. FDA stated that the commitment would be taken into consideration in determining the approvability of NDA 206321 for Saxenda.

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/s/

JULIE C VAN DER WAAG
12/04/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 20, 2014
Application Number: NDA 206321
Product Name: Saxenda (liraglutide injection), 3 mg
Sponsor/Applicant Name: Novo Nordisk, Inc
Subject: Saxenda Action Date Delay

FDA Participants

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
James P. Smith, M.D., M.S.	Deputy Director (Acting)
Jennifer Pippins, M.D.	Deputy Director for Safety
Pat Madara, M.S.	Project Manager

Novo Nordisk Participants

Robert B. Clark	US Regulatory Affairs
Robin P. Evers	Global Regulatory Affairs
Anne Phillips	Clinical, Medical and Regulatory Affairs
Peter Kristensen	Global Development
Mads Krogsgaard Thomsen	Research & Development
Heather Millage	Project Management
Peter Schelde	Project Management
Christine Bjorn Jensen	Project Director
Stephanie DeChiaro	US Regulatory Affairs
Michelle Thompson	US Regulatory Affairs

1.0 Background:

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist that was approved for the treatment of type 2 diabetes in 2010 (Victoza, NDA 22341), at 1.2 mg and 1.8 mg daily doses.

Liraglutide (Saxenda, NDA 206321) is currently under review at a 3 mg daily dose as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Victoza was approved with a Boxed Warning and a REMS to address the potential risk of medullary thyroid carcinoma and the risk of pancreatitis. The same Boxed Warning and REMS are recommended for Saxenda.

Saxenda was submitted on December 20, 2014, and the PDUFA goal date is October 20, 2014.

On Friday, October 17, 2014, CDER management held an internal meeting to discuss Novo Nordisk's lack of compliance with the Victoza REMS. It was decided that Saxenda should not be approved until CDER management had the opportunity to address their concerns with Novo Nordisk. Furthermore, CDER management requested additional internal review of the REMS. Therefore, it was decided that no action could be taken on NDA 206321 until further notice.

2.0 Discussion:

FDA informed Novo Nordisk that on Friday, CDER management had raised some issues regarding the proposed REMS. Because of this, the Division could not take an action on the application and it would go overdue.

The Division explained that they were not at liberty to discuss the issues. It was hoped that they would be addressed within a few days, but since the Division is relying on input from other groups within FDA, the timeline was uncertain and the Division could not speculate on a potential date for an action. The Division reiterated that they were restrained in what information could be shared.

Novo Nordisk stated that they understood that senior management had some questions regarding the REMS and details could not be shared.

It was confirmed that the review Division did not require any additional information from the company. Others within the Agency were discussing the REMS, and the Division would let Novo Nordisk know when they had clearance to share information.

The company asked whether agreement had been reached on all other items of the application, such as labeling and postmarketing requirements/commitments. The Division stated that, at this time, it appeared that there were no outstanding issues with those items.

Novo Nordisk noted that they had a responsibility to communicate publically but did not want to misrepresent the situation. The company asked if the Division would like to review a draft press release. DMEP commented that they were hesitant to review press announcements, as the Division does not "clear" press releases, and a lack of comment could be misconstrued as FDA approval of the press release. The Division reiterated that the timeline was uncertain, and emphasized that an eventual action may not necessarily be an approval action, despite the fact that we have negotiated labeling and postmarketing requirements/commitments. The firm confirmed their understanding.

The teleconference ended.

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/s/

JEAN-MARC P GUETTIER
11/25/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Request for Information
Date: Friday, October 17, 2014 9:16:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

In addition, we reference your email dated October 16, 2014, containing the SAS program codes we had requested. We have reviewed the submission and have the following comment and request for information.

- **We are unable to replicate results in Table 4 for the most recent label. In particular:**

1. **For Trial 1839 we could not replicate your results. We suspect this may be related to an issue described in a 6/26/2014 information request. Please submit a revised SNFB analysis dataset that has corrected values for the topic codes:**

(b) (4)

2. **For Trial 1922 we obtained a different 95% CI for the 5% response endpoint. Please confirm whether the CI in the Table is correct. The CI we obtained was (25.1, 40.1).**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/30/2014

From: Madara, Patricia
To: ["MTHO \(Michelle Thompson\)"](#)
Subject: RE: NDA 206325 (Saxenda) labeling revision request and Information Request
Date: Thursday, October 23, 2014 1:51:00 PM
Importance: High

NDA 206321

ADVICE / INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity) Injection.

We have reviewed your request for revisions to the package insert described below and have the following recommendations

1. Your request for the following change is acceptable:

"In clinical trials, 9.8% of patients treated with Saxenda and (b) (4) 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for Saxenda and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%)."

2. With regard to the 2nd revision in Section 6, Adverse Reactions, laboratory abnormalities, we would prefer the following language:

"Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15% (b) (4) Saxenda-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo-treated patient during the Saxenda clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to Saxenda is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones)."

In addition, we have the following comment and request for information:

1. **Two cases of injection site panniculitis, in both cases leading to discontinuation, were noted. Were these cases included with the tallies of injection site reactions and discontinuations due to injection site reactions? If not, please update the percentages in the label.**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

From: MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]
Sent: Monday, October 20, 2014 3:27 PM
To: Madara, Patricia
Subject: NDA 206325 (Saxenda) Follow-up to our tcon earlier today

Hi Pat,

Majorly disappointed as you can imagine☹ I hope you at least can go home and recover from you bad cough/cold. Here is a list of NN participants on today's call:

Robert B. Clark	US Regulatory Affairs
Robin P. Evers	Global Regulatory Affairs
Anne Phillips	Clinical, Medical and Regulatory Affairs
Peter Kristensen	Global Development
Mads Krogsgaard Thomsen	Research & Development
Heather Millage	Project Management
Peter Schelde	Project Management
Christine Bjorn Jensen	Project Director
Stephanie DeChiaro	US Regulatory Affairs
Michelle Thompson	US Regulatory Affairs

As we were waiting to hear from you we were doing a last minute check of the PI and discovered the following errors, can you please confirm that we can go ahead and make these changes?

In Section 6, Adverse Reactions, above table 3, should be 4.3% of patients based on the ISS, Appendix 7.2, 32

- In clinical trials, 9.8% of patients treated with Saxenda and (b) (4) 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for Saxenda and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%).

In Section 6, Adverse Reactions, laboratory abnormalities, should be 0.1% of patients based on response submitted on September 26th response (sequence 37, Module 1.11.4, Appendix, Table 1) to the September 23rd IR

- Liver Enzymes

Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 ((b) (4) Saxenda-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (b) (4) placebo-treated patient during the Saxenda clinical trials. Because clinical evaluation to

exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to Saxenda is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).

Also if you can let us know when you want us to formally submit a clean copy through the Gateway, it would be much appreciated. Thanks Pat, and as always if you have any questions please give me a call.

Michelle

Michelle Thompson

Senior Director, Regulatory Affairs
Clinical Development, Medical & Regulatory Affairs

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
USA
609-987-5972 (direct)
[REDACTED] (b)(6) (mobile)

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PATRICIA J MADARA
10/24/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) - PMRs and PMC dates - minor revisions
Date: Thursday, October 16, 2014 11:24:00 PM
Attachments: [FDA to NN_16Oct14_PMR and PMC Dates.doc](#)
Importance: High

Hi Michelle;

During our internal PMR/PMC clearance process, some minor changes to the PMR descriptions were made – please see attached document, with the changes tracked.

Please confirm receipt and concurrence. Thanks.

Sincerely;

Pat Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

**PMR/PMC list for NDA 206321
SAXENDA (liraglutide) injection**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity.

Final Report Submission: November 2014

2. A clinical pharmacology (b) (4)-study (Trial NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

Final Report Submission: December 2014

3. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

Final Protocol Submission: August 2015

Trial Completion: August 2019

Final Report Submission: August 2020

4. A clinical pharmacology (b) (4)-study to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

Final Protocol Submission: September 2015

Trial Completion: August 2017

Final Report Submission: February 2018

5. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The trial may not be initiated until results from the Saxenda adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission: April 2020
Trial Completion: October 2023
Final Report Submission: August 2024

6. A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Saxenda (liraglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Saxenda (liraglutide).

Final Protocol Submission: June 2015
Trial Completion: September 2030
Final Report Submission: September 2031

7. To assess the risk of breast cancer associated with liraglutide in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) cardiovascular outcomes trial. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the-^{(b) (4)} trial-^{(b) (4)} including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Final Protocol Submission: December 2014
Trial Completion: September 2015
Final Report Submission: April 2016

8. To assess the risk of breast cancer associated with liraglutide in Trial 1839. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial^{(b) (4)} including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Final Protocol Submission: December 2014
Trial Completion: February 2015
Final Report Submission: August 2015

Postmarketing Commitments:

9. A study evaluating gallbladder ejection fractions in liraglutide treated subjects to further characterize the effect of liraglutide on gallbladder motility.

Final Protocol Submission:	September 2015
Trial Completion:	January 2017
Final Report Submission:	September 2017

Please note: The following post-marketing requirement for Victoza (liraglutide), 1.8 mg will be included in the action letter for Saxenda (liraglutide), 3 mg:

PMR 1583-9 A randomized, double-blind, controlled trial evaluating the effect of liraglutide on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus and including measurement of calcitonin, a biomarker for medullary thyroid carcinoma.

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/s/

PATRICIA J MADARA
10/20/2014

From: Madara, Patricia
To: "MTHO (Michelle Thompson)"
Subject: RE: NDA 206321 (Saxenda) Revised MG and IFU
Date: Friday, October 17, 2014 10:58:00 AM
Attachments: [FDA to NN_17Oct14_NN_Revisions_only.doc](#)
Importance: High

Hi Michelle;

We have reviewed your proposed revisions to the medication guide and instructions for use. [We agree with all your proposals for the medication guide.](#)

Regarding the IFU, we disagree with your proposal (b) (4). They are unacceptable for the following reasons:

1. (b) (4) are confusing and people with lower reading comprehension will probably not understand them.
2. Their use is not consistent with patient labeling practice.

We suggest that you incorporate standard "numbering" of the figures but retain the circled "i" in the left hand margin.

I have attached the IFU that you sent to us (no FDA revisions). Please let me know if the changes above are acceptable.

Sincerely;

Pat Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]
Sent: Thursday, October 16, 2014 3:44 PM
To: Madara, Patricia
Subject: RE: NDA 206321 (Saxenda) Revised MG and IFU

Hi Pat,

Attached are the NN comments to the Saxenda Med Guide and IFU. We have accepted most of the changes with a few exceptions. We will not submit through the gateway 'officially' until you tell us to go ahead. Let me know if you have any questions.

Still working on REMS to get back to you today. Thank you.

Michelle

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Wednesday, October 15, 2014 9:12 PM
To: MTHO (Michelle Thompson)
Subject: NDA 206321 (Saxenda) Revised MG and IFU
Importance: High

Hi Michelle;

I am enclosing the medication guide (MG) and instructions for use (IFU) for Saxenda, containing FDA revisions. Almost all these revisions were made by the patient labeling team.

In addition to content, they may make revisions to the format of the documents. Please use the versions attached to this email, if you need to make additional changes. Apparently attempting to copy and paste formatting revisions into another document can result in loss of the changes (including the font, bulleting, indentation, and line spacing).

If you have any questions or do not agree with any of the revisions, please send me your edits and we will discuss with the patient labeling team. They have revised the documents to help ensure patient comprehension and they are experts at this. As before, accept all the revisions with which you agree. If you want to propose alternative language, leave our track changes and add your own edits in track changes also.

The REMS documents have not cleared final review and sign off. I will send them as soon as possible.

Please contact me if you have any questions. Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Phone: 301-796-1249

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/s/

PATRICIA J MADARA
10/20/2014

From: Madara, Patricia
To: "[MTHO \(Michelle Thompson\)](#)"
Subject: RE: NDA 206321 (Saxenda) - Clarification requested on a comment in PI from the Toxicology review
Date: Friday, October 17, 2014 11:03:00 AM
Importance: High

Hi Michelle;

The nonclinical team provides the following explanation:

- **Novo Nordisk is using AUC(inf) (table on page 1586 of report 200240) to calculate exposure multiples, but FDA is using AUC(tau)(Table 2 on page 1597), the AUC during the dosing interval. In the rat carcinogenicity study, blood samples for toxicokinetic analyses were taken prior to dosing (0) and 1, 2, 4, 6, 8, 12, and 24 hours after dosing in week 104. The dosing regimen in the rat carcinogenicity study was 1 injection every 24 hours, so AUC(tau) should be equal to (or very close to) AUC(0-24h). Human exposure multiples were calculated using AUC(0-24h), when available.**
- **In the rat carcinogenicity study using doses of 0.075, 0.25, and 0.75 mg/kg/day liraglutide, systemic exposures were 0.5-, 2-, and ^(b)₍₄₎ times human exposure, respectively, based on AUC comparison.**

Please let me know if you require any additional clarification.

Sincerely;

Pat Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]
Sent: Friday, October 17, 2014 9:59 AM
To: Madara, Patricia
Subject: NDA 206321 (Saxenda) - Clarification requested on a comment in PI from the Toxicology review

Hi Pat,

The PI in Section 13.1 reads "A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and ^(b)₍₄₎ times the exposure in obese humans, respectively, resulting from the MRHD based on plasma AUC

comparison." and FDA made a comment "FDA comment: In rats, week 104 plasma AUC(0-24h)s were [REDACTED] (b) (4) nM*h in 0.075, 0.025, and 0.75 mg/kg/day liraglutide groups (average of males and females combined), respectively."

When we look into report 200240 (on page 1586) in the TK table we get:

[REDACTED] (b) (4)

We would like to understand how the reviewer determined the exposure ratio, as it is different than our calculation. Would it be possible to get clarification from the Tox reviewer? Thanks so much for your help.

Michelle

Michelle Thompson

Senior Director, Regulatory Affairs
Clinical Development, Medical & Regulatory Affairs

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
USA
609-987-5972 (direct)
[REDACTED] (b) (6) (mobile)

This e-mail (including any attachments) is intended for the addressee(s) stated above only and may contain confidential information protected by law. You are hereby notified that any unauthorized reading, disclosure, copying or distribution of this e-mail or use of information contained herein is strictly prohibited and may violate rights to proprietary information. If you are not an intended recipient, please return this e-mail to the sender and delete it immediately hereafter. Thank you.

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/s/

PATRICIA J MADARA
10/20/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) - minor revision based on review of antibody formation data
Date: Friday, October 17, 2014 12:40:00 PM
Importance: High

Hi Michelle;

Reference your amendment to NDA 206321, on October 15, 2014, containing additional information related to antibody formation associated with liraglutide use. We have reviewed the submission and based on the data we are requesting a minor revision to the package insert as described below (underline and strike out):

Immunogenicity

Patients treated with Saxenda may develop anti-liraglutide antibodies. Anti-liraglutide antibodies were detected in 42 (2.8%) of 1505 Saxenda-treated patients with a post-baseline assessment. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 18 (1.2%) of 1505 Saxenda-treated patients. Presence of antibodies may be associated with a higher incidence of injection site reactions [REDACTED] (b) (4) and reports of low blood glucose. In clinical trials, these events were usually classified as mild and resolved while patients continued on treatment.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to Saxenda cannot be directly compared with the incidence of antibodies of other products.

Please let me know if you have any questions or concerns about this change. Many thanks. Pat

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/s/

PATRICIA J MADARA
10/20/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) Revised MG and IFU
Date: Wednesday, October 15, 2014 9:11:00 PM
Attachments: [FDA to NN 15Oct14 IFU.doc](#)
[FDA to NN 15Oct14 MG.doc](#)
Importance: High

Hi Michelle;

I am enclosing the medication guide (MG) and instructions for use (IFU) for Saxenda, containing FDA revisions. Almost all these revisions were made by the patient labeling team.

In addition to content, they may make revisions to the format of the documents. Please use the versions attached to this email, if you need to make additional changes. Apparently attempting to copy and paste formatting revisions into another document can result in loss of the changes (including the font, bulleting, indentation, and line spacing).

If you have any questions or do not agree with any of the revisions, please send me your edits and we will discuss with the patient labeling team. They have revised the documents to help ensure patient comprehension and they are experts at this. As before, accept all the revisions with which you agree. If you want to propose alternative language, leave our track changes and add your own edits in track changes also.

The REMS documents have not cleared final review and sign off. I will send them as soon as possible.

Please contact me if you have any questions. Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
10/16/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) REMS documents
Date: Thursday, October 16, 2014 10:57:00 AM
Attachments: [FDA to NN 16Oct14 proposed-rems-support-tracked.doc](#)
[FDA to NN 16Oct14 DRISK REMS comments.docx](#)
[FDA to NN 16Oct14 proposed-rems-tracked.doc](#)
[FDA to NN 16Oct14 REMS slides revised.pptx](#)
Importance: High

Hi Michelle;

I am enclosing the revised REMS documents.

If you have any questions or do not agree with any of the revisions, please send your edits via email and we will discuss with the safety labeling team and DRISK.

DRISK has requested that you submit any proposed changes via email only so that the next official submission can be considered final.

Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
10/16/2014

From: Madara, Patricia
To: ["MTHO \(Michelle Thompson\)"](#)
Subject: RE: NDA 206321 (Saxenda) REMS documents
Date: Thursday, October 16, 2014 7:47:00 PM
Attachments: [FDA to NN_16Oct14_NN to FDA_15Oct14.doc](#)
Importance: High

Hi Michelle;

I have attached the revised PI, taking into account your proposed edits below. It does not include your revisions to Table 1 in section 14, sent to us, via email, at 6:33 PM. I will forward those changes to the statistical review team.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]
Sent: Thursday, October 16, 2014 2:45 PM
To: Madara, Patricia
Subject: RE: NDA 206321 (Saxenda) REMS documents

Hi Pat,

Please see below proposed text from NN related to description of glycemia and proposal for placement in sections 5, 6 and 12. We are working on the data table for section 14 and should have it too you shortly.

Thanks for the information re the REMS documents, we are working on these and should have them to you soon. Let me know if you have any other questions.

Michelle

Section 5.4 Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy

The risk for serious hypoglycemia is increased when Saxenda is used in combination with insulin secretagogues (for example, sulfonylureas) in patients with type 2 diabetes mellitus. Therefore, patients may require a lower dose of sulfonylurea (or other concomitantly administered insulin secretagogues) in this setting [*see Dosage and Administration (2) and Adverse Reactions (6.1)*].

Saxenda should not be used in patients taking insulin.

(b) (4)

Section 6 (b) (4)

Novo Nordisk Comment: Novo Nordisk believes (b) (4)

In a clinical trial involving patients with overweight or obesity and concomitant type 2 diabetes mellitus (b) (4) severe hypoglycemia

(defined as requiring the assistance of another person) occurred in 3 (0.7%) of 422 Saxenda-treated patients and in none of the 212 placebo-treated patients. Each of these 3 Saxenda-treated patients was also taking a sulfonylurea. In the same trial, among patients taking a sulfonylurea, documented symptomatic hypoglycemia (defined as documented symptoms of hypoglycemia in combination with a plasma glucose less than or equal to 70 mg/dL) occurred in 48 (43.6%) of 110 Saxenda-treated patients and 15 (27.3%) of 55 placebo-treated patients. The doses of sulfonylureas were reduced by 50% at the beginning of the trial per protocol. The frequency of hypoglycemia may be higher if the dose of sulfonylurea is not reduced. Among patients not taking a sulfonylurea, documented symptomatic hypoglycemia occurred in 49 (15.7%) of 312 Saxenda-treated patients and 12 (7.6%) of 157 placebo-treated patients.

In Saxenda clinical trials involving patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia, as patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of unconfirmed hypoglycemia were reported by 46 (1.6%) of 2962 Saxenda-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fasting plasma glucose values obtained at routine clinic visits less than or equal to 70 mg/dL, irrespective of hypoglycemic symptoms, were reported as "hypoglycemia" in 92 (3.1%) Saxenda-treated patients and 13 (0.8%) placebo-treated patients.

Section 12.1 Pharmacodynamics

Liraglutide lowers body weight through decreased calorie intake. Liraglutide does not increase 24-hour energy expenditure.

As with other GLP-1 receptor agonists, liraglutide stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner. These (b) (4) effects (b) (4)

Cardiac Electrophysiology (QTc) in healthy volunteers

The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steady-

state concentrations after daily doses up to 1.8 mg did not produce QTc prolongation. The maximum liraglutide plasma concentration (C_{max}) in overweight and obese subjects treated with liraglutide 3 mg is similar to the C_{max} observed in the liraglutide QTc study in healthy volunteers.

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Thursday, October 16, 2014 2:28 PM
To: MTHO (Michelle Thompson)
Subject: RE: NDA 206321 (Saxenda) REMS documents
Importance: High

Hi Michelle;

I checked with DRISK and all the items you mention are appended to the REMS supporting document since that was the way you sent them to us. DRISK did say it might be easier if each was a separate item.

Also, they mentioned that you should make sure everything is aligned with the most recent label.

Finally, we will be sending the PI to you shortly, with our revisions (discussed and not discussed at the tcon). I am not sure we will be able to include the sections you are sending to us.

We will see what happens. Pat

From: MTHO (Michelle Thompson) [<mailto:mtho@novonordisk.com>]
Sent: Thursday, October 16, 2014 11:29 AM
To: Madara, Patricia
Subject: RE: NDA 206321 (Saxenda) REMS documents

Hi Pat,

Thanks for sending. You did not include the REMS Letters or Factsheet. Can I go ahead and revise based on the comments in the attached documents (as well as to update the indication per the current draft label)? And then we can return all these to you. Let me know thanks.

Michelle

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Thursday, October 16, 2014 10:57 AM
To: MTHO (Michelle Thompson)
Subject: NDA 206321 (Saxenda) REMS documents
Importance: High

Hi Michelle;

I am enclosing the revised REMS documents.

If you have any questions or do not agree with any of the revisions, please send your

edits via email and we will discuss with the safety labeling team and DRISK.

DRISK has requested that you submit any proposed changes via email only so that the next official submission can be considered final.

Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
10/16/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide) - safety labeling changes
Date: Tuesday, October 07, 2014 4:18:00 PM
Attachments: [FDA to NN_7Oct14-physician-insert_WORD.doc](#)

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

In addition, we reference the draft, revised package insert we sent to you via email on September 30, 2014 and the response you sent today, via email.

Please see the revisions – ONLY THOSE ITEMS HIGHLIGHTED IN BRIGHT GREEN - to the package insert attached to this email.

Please incorporate these revisions into your most recent version of the PI (i.e. the one just sent to us) and send back via email. They are revisions requested as part of a class labeling change for all long-acting GLP-1 agonist products.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/13/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide) - safety labeling changes
Date: Tuesday, October 07, 2014 4:18:00 PM
Attachments: [FDA to NN_7Oct14-physician-insert_WORD.doc](#)

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

In addition, we reference the draft, revised package insert we sent to you via email on September 30, 2014 and the response you sent today, via email.

Please see the revisions – **ONLY THOSE ITEMS HIGHLIGHTED IN BRIGHT GREEN** - to the package insert attached to this email.

Please incorporate these revisions into your most recent version of the PI (i.e. the one just sent to us) and send back via email. They are revisions requested as part of a class labeling change for all long-acting GLP-1 agonist products.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/13/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide) - FDA revisions
Date: Monday, October 13, 2014 1:57:00 PM
Attachments: [FDA to NN_13Oct_NN to FDA_8Oct14.doc](#)
Importance: High

NDA 206321

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

In addition, we reference the draft, revised package insert you sent to us via email on October 8, 2014. We have reviewed your proposed changes and responded.

Please incorporate our revisions into the most recent version of the PI.
Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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PATRICIA J MADARA
10/13/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda) Revisions to PMRs and PMC requested
Date: Wednesday, October 08, 2014 3:48:00 PM
Attachments: [FDA to NN_08oct14_Reponse to Company's Oct 3 PMR submission SAXENDA.doc](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide) Injection.

In addition we reference the draft milestone dates for PMRs and PMCs that you submitted on October 3, 2014.

We have reviewed your proposed dates and request some revisions. Please correct the dates as indicated in the attached document, in track changes.

Please submit the revisions via email, as an MS WORD document in track changes. Please provide your responses by COB tomorrow (10/9/14)

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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PATRICIA J MADARA
10/08/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Revisions to REMS materials
Date: Monday, September 29, 2014 1:51:00 PM
Attachments: [FDA to NN 2014 09 29 Saxenda NDA 206321 REMS comments.pdf](#)
[FDA to NN 2014 09 29 Liraglutide 3.0 mg REMS.doc](#)
[FDA to NN 2014 09 29 Liraobesity REMS Supporting Doc.doc](#)
[FDA to NN 2014 09 29 REMS Factsheet.docx](#)
[FDA to NN 2014 09 29 REMS Letter for HCP.docx](#)
[FDA to NN 2014 09 29 REMS Letter for Prof Society.docx](#)
[FDA to NN 2014 09 29 REMS slides.pptx](#)
[FDA to NN 2014 09 29 REMS WEBSITE.docx](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application. We are sending revised REMS materials for review. Our comments are contained in the attached PDF document.

Please remember that additional changes to the REMS may be required to align REMS-related documents with the final version of the label.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/03/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - request for Information
Date: Thursday, October 02, 2014 10:34:00 AM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application and have the following request for information.

- **We note that in your briefing document for the September 11, 2014, advisory committee meeting that “[o]ne MTC event has occurred in the ongoing LEADER trial, treatment allocation remains blinded” (p. 180). Please unblind this case and provide us with a safety report and relevant case report forms. Please include available clinical information that could aid in a causality assessment such as demographics, calcitonin data, any genetic testing (*RET*) performed, past medical history, family history, pathology reports, and staging. If other cases of MTC have been reported in LEADER since your briefing document was written, please unblind these cases and provide the same information.**
- **Please respond to this request with available information by COB October 3, 2014; if time is needed to gather additional follow-up information, provide your anticipated timeline for a subsequent response.**

Thanks for your help. [Please confirm receipt of this email.](#)

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/02/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Information request and FAERS safety report
Date: Tuesday, September 30, 2014 10:12:00 AM
Attachments: [30sept14_Victoza_CaseRedacted.pdf](#)
Importance: High

NDA 206321

ADVICE / INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following request for information.

- **Please provide all available follow up information on patient 425011 from trial 3970. His AST was 381 and ALT was 165 at week 4 and then he discontinued the trial.**

In addition, we have attached a copy of the safety report you requested via email, on September 24, 2014. This case was submitted directly to FDA so the attached version is redacted.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Individual Case Safety Report



10258145-01-00-01

Professional Report

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Reporting of adverse events and product use errors

FDA USE ONLY

Triage unit sequence # **554758**

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier [Redacted]	2. Age at Time of Event or Date of Birth: 66 Years	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 267 lb or _____ kg
-------------------------------------	---	---	------------------------------------

In confidence

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. Adverse Event Product Problem (e.g., defects/malfunctions)
 Product Use Error Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)

Death: _____ (mm/dd/yyyy) Disability or Permanent Damage
 Life-threatening Congenital Anomaly/Birth Defect
 Hospitalization - initial or prolonged Other Serious (Important Medical Events)
 Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) 4. Date of this Report (mm/dd/yyyy)
04/24/2014 06/20/2014

5. Describe Event, Problem or Product Use Error
Medullary thyroid carcinoma

6. Relevant Tests/Laboratory Data, including Dates
Calcitonin level ...

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
no family history of multiple endocrine neoplasia related disease

CTU
JUN 23 2014

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

Yes No Returned to Manufacturer on: _____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 Name: victoza
Strength: 1.8 mcg
Manufacturer: Novo Nordisc

#2 Name:
Strength:
Manufacturer:

CTU
JUN 24 2014

2. Dose or Amount	Frequency	Route
#1 1.8 mcg	OD	Subcutaneous
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)

#1 04/04/2012 - 04/12/2014

#2

4. Diagnosis or Reason for Use (Indication)

#1 type 2 diabetes

#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 Yes No Doesn't Apply

#2 Yes No Doesn't Apply

6. Lot # 7. Expiration Date

#1 11111 #1

#2 #2

8. Event Reappeared After Reintroduction?

#1 Yes No Doesn't Apply

#2 Yes No Doesn't Apply

9. NDC # or Unique ID

1111

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model # Lot # 5. Operator of Device
 Health Professional

Catalog # Expiration Date (mm/dd/yyyy) Lay User/Patient

Serial # Other # Other:

6. If Implanted, Give Date (mm/dd/yyyy) 7. If Expired, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
 Yes No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
JUN 23 2014

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)
aspirin, avapro, citalopram, coQ10, Fish oil, flax seed, Glucotrol XL, HCTZ, Levemir, Livalo, Multivitamin, ...

G. REPORTER (See confidentiality section on back)

1. Name and Address

Name: [Redacted]
Address: [Redacted]
City: [Redacted] State: [Redacted] ZIP: [Redacted]

Phone # [Redacted] E-mail [Redacted]

2. Health Professional? 3. Occupation 4. Also Reported to:

Yes No Medical Doctor (Physician) Manufacturer
 User Facility
 Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:

PLEASE TYPE OR USE BLACK INK

554758

B.6. Relevant Tests/Laboratory Data, Including Dates (continued)

... 976. Pathology from [REDACTED] thyroidectomy: Medullary thyroid carcinoma, 2.8 cm 1 of 33 lymph nodes positive.
RET mutation C2372A>T

Individual Case Safety Report



10258145-01-00-02

DSS
JUN 23 2014

004108

B.7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)

...case

Individual Case Safety Report



10258145-01-00-03

DSS
JUN 23 2014

554758

F. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) (continued)

... Omeprazole, Tricor, Vitamin D

Individual Case Safety Report



10258145-01-00-04

DSS
JUN 23 2014

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/s/

PATRICIA J MADARA
09/30/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Saxenda prescriber information with FDA revisions
Date: Tuesday, September 30, 2014 9:04:00 PM
Attachments: [1839 mi 5 percent responder.do](#)
[1839 mi 10 percent responder.do](#)
[1839 mi absolute change.do](#)
[1839 mi emperical distribution plot.do](#)
[1839 mi percent change.do](#)
[1922 mi 5 percent responder.do](#)
[1922 mi 10 percent responder.do](#)
[1922 mi absolute change.do](#)
[1922 mi percent change.do](#)
[1923 weighted absolute and percent change.do](#)
[1923 weighted categorical analysis .do](#)
[SRPI.pdf](#)
[FDA to NN_30Sept14-physician-insert_WORD.doc](#)

Importance: High

Hi Michelle;

I am enclosing the package insert for Saxenda, containing FDA revisions. Please review our tracked changes. I recommend you accept all our revisions (but do not delete our comments). If you feel strongly that something should be added or deleted or revised, please leave our revisions, add your changes and provide a robust rationale.

Please note the label remains under review and additional changes may be forthcoming; for example, we have not completed our review of Section 5.1. In addition, the patient labeling team has not yet reviewed the Medication Guide and Instructions for Use.

I am also attaching the following items:

1. "The Selected Requirements of Prescribing Information." It is a checklist to ensure that the PI complies with the PLR requirements. This form used to be completed (and revisions requested) by the reviewing division. It is now the responsibility of the company.
2. The program codes used for our statistical analysis.
3. The following general revisions should be incorporated throughout the labeling (Carton Labeling, Pen Label, Package Insert Labeling, and IFU), wherever they are applicable, if not already corrected.
 - a. If there are any instances of the symbol '<' or '>' anywhere in the labeling, revise to use appropriate wording. The 'greater than' and 'less than' symbols are dangerous abbreviations that could be interpreted opposite of its intended meaning.
 - b. Remove all trailing zeros throughout the label and labeling, if we have not already deleted them. The trailing zero after the decimal point may lead to misinterpretation (e.g. 3.0 mg as 30 mg). Trailing zeros are listed as a

dangerous dose designation on the Institute of Medicine's 'List of Error-Prone Abbreviations, Symbols, and Dose Designations'. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.

4. Please determine if the length of the Saxenda highlights (HL) is greater than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If it is, please request a waiver or let me know where the waiver request is located within your application.

Please contact me if you have any questions. Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Please confirm receipt.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

43 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA J MADARA
09/30/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 Saxenda (liraglutide for obesity) - request for information
Date: Friday, September 26, 2014 3:05:00 PM

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Yes, I'm back. Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application and have the following request for information.

- **Please comment on patients with treatment emergent CK > 10x ULN. Did any patient experience CK above this value in association with muscle symptoms and/or creatinine increases that would be suggestive of myopathy? How many patients with CK > 10x ULN had an alternative explanation for the increase, such as vigorous exercise (if known)?**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
09/26/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: FW: NDA 206321 (Saxenda, liraglutide for obesity) Request for Information - clarification
Date: Thursday, September 25, 2014 11:34:00 AM
Attachments: [23Sept14_clinical_IR.pdf](#)
Importance: High

Hi Michelle;

For the information request below, the clinical review team has the following clarification:

- **Data for patients in 1807 ext 2 should be included with the treatment received at the time of the event, rather than according to treatment randomization (in other words, a patient who was randomized to placebo, but has ALT > 3x ULN on liraglutide in year 2, should be counted as a lira patient).**

Please contact me if you have any questions.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Madara, Patricia
Sent: Tuesday, September 23, 2014 8:33 PM
To: MTHO (Michelle Thompson) (mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda, liraglutide for obesity) Request for Information
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application and have an additional request for information.

- **Please respond to the request contained in the attached PDF document.**

You may respond unofficially, via email, but also submit the information officially to your NDA.

Note we are requesting submission of the information by September 26, 2014, or, if necessary, by September 29, 2014, at the very latest.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
09/25/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Request for Information
Date: Thursday, September 25, 2014 12:23:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application and have the following request for information.

- **Are the patients identified as ‘no antibodies’ in table 2-106 known to have no antibodies, or are you also including patients who weren’t tested / only had baseline assessments? If the latter, please recalculate the AE incidences for ‘no antibodies’ using the correct denominator (as per table 2-105).**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
09/25/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 Saxenda (liraglutide for obesity)
Date: Thursday, September 25, 2014 11:52:00 AM
Attachments: [FDA to NN_25sept14_SAXENDA - PMRs and PMCs.doc](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide) Injection.

We continue to review your application. Please find attached a draft list of postmarketing required studies and postmarketing commitments.

We request that you provide milestone dates for each study and return the document to us. **Please respond as soon as possible but no later than October 1, 2014.**

You may submit your responses informally, however, when agreement has been reached, please submit the milestone dates officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**PMR/PMC list for NDA 206321
SAXENDA (liraglutide) injection**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity.

Trial Completion:

Final Report Submission:

2. A clinical pharmacology trial (Trial NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

Trial Completion:

Final Report Submission:

3. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

Final Protocol Submission:

Trial Completion:

Final Report Submission:

4. A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

Final Protocol Submission:

Trial Completion:

Final Report Submission:

5. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The trial may not be initiated until results from the Saxenda adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

6. A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Saxenda (liraglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Saxenda (liraglutide)

Final Protocol Submission:

Trial Completion:

Final Report Submission:

7. To assess the risk of breast cancer associated with liraglutide, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the cardiovascular outcomes trial (LEADER), including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

8. To assess the risk of breast cancer associated with liraglutide, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in Trial 1839, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Postmarketing Commitments:

9. A study evaluating gallbladder ejection fractions in liraglutide treated subjects to further characterize the effect of liraglutide on gallbladder motility.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

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/s/

PATRICIA J MADARA
09/25/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda, liraglutide for obesity) Request for Information
Date: Tuesday, September 23, 2014 8:33:00 PM
Attachments: [23Sept14_clinical_IR.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxenda (liraglutide for obesity).

We continue to review your application and have an additional request for information.

- **Please respond to the request contained in the attached PDF document.**

You may respond unofficially, via email, but also submit the information officially to your NDA.

Note we are requesting submission of the information by September 26, 2014, or, if necessary, by September 29, 2014, at the very latest.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We recently became aware of a patient (trial 1839, ID 473005), who had elevations in transaminases and lipase at unscheduled visits (e.g., day 48, ALT 328 U/L; day 56 ALT 83 U/L). The reason provided that these values were not included in reporting was, 'Not selected retest' (DFLAGR variable).

Finding this patient whose ALT and AST values at these unscheduled visits were not reported in the CSR and not captured in outlier analyses (e.g., in the response to FDA request dated 18 Jun 2014), gives us concern that there are cases that may have been missed.

Therefore, we request that you recalculate the outlier information from your response to FDA request dated 18 Jun 2014 for the following parameters utilizing all treatment-emergent study values in the database, including unscheduled visits:

ALT
≥ 3x ULN
≥ 5x ULN
≥ 10x ULN
≥ 20x ULN
AST
≥ 3x ULN
≥ 5x ULN
≥ 10x ULN
≥ 20x ULN
Alk Phos
≥ 2.5x ULN
≥ 5x ULN
≥ 20x ULN
T. bili
≥ 1.5x ULN
≥ 2x ULN
≥ 3x ULN
≥ 10x ULN
ALT + T. bili
ALT > 3x ULN + T. bili > 2x ULN
Serum creatinine
≥ 0.3 mg/dL increase from baseline
≥ 1.5x baseline
≥ 3x baseline

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/s/

PATRICIA J MADARA
09/23/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: RE: NDA 206321 (Saxenda, liraglutide for obesity) - REQUEST FOR INFORMATION
Date: Friday, September 19, 2014 4:19:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle;

As a follow-up to the requests listed below, we also have an additional request for information.

- **Provide the percentage of patients lost to follow-up in the LEADER trial to date by September 24, 2014.**

Thanks again for your help. Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: Madara, Patricia
Sent: Friday, September 19, 2014 3:49 PM
To: MTHO (Michelle Thompson) (mtho@novonordisk.com)
Subject: NDA 206321 (Saxenda, liraglutide for obesity) - REQUEST FOR INFORMATION
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following requests for information.

1. **Provide the number of breast cancer cases identified to date in the**

LEADER trial, by blinded treatment allocation (i.e., A vs. B). Provide the number of events sent for adjudication, the number of positively adjudicated malignant events, and the number of suspected or pending cases that have not yet been reviewed by the adjudication committee.

- 2. Provide median and cumulative patient-years of follow-up in the ITT population (i.e., regardless of ongoing drug exposure status) by blinded treatment allocation (i.e., A vs. B) to date in the LEADER trial.**
- 3. Provide the most updated counts of breast cancer cases and event rates from the ongoing extension of trial 1839. Provide the number of events sent for adjudication, the number of positively adjudicated malignant events, and the number of suspected or pending cases that have not yet been reviewed by the adjudication committee.**
- 4. Explain your procedures to ensure cancer ascertainment in patients who don't return to follow-up visits for both LEADER and 1839-ext.**

We request the answers to questions #1-3 by 9/24 and question #4 by 10/1.

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
09/19/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) urgent requests for information
Date: Thursday, August 28, 2014 8:06:00 PM
Importance: High

NDA 206321

URGENT INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We have the following comments and urgent requests for information.

1. The footnote of figure 2-57 of the ISS states that “curves represent mean for subjects with no adjudicated breast neoplasms”. Does “subjects” refer to all subjects or just women?

In addition, we reference the briefing document you submitted for the upcoming advisory committee meeting.

2. On page 180 paragraph 2, you make the following statement: “***In the postmarketing setting, 12 spontaneous reports of MTC have been observed with Victoza® as of 30 June 2014 based on more than 3.3 million PYE.***”

Please supply the following information on the 12 spontaneous reports you reference:

- a. **Manufacturer Control Number:**
- b. **Date of Submission to the FDA:**
- c. **Event Verbatim (Preferred Terms):**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/29/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Urgent request for information
Date: Tuesday, August 12, 2014 1:16:00 PM
Importance: High

NDA 206321

URGENT INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity. In addition, we reference the briefing document you just submitted for the upcoming advisory committee meeting

We have the following comments and urgent requests for information.

Please respond by close of business on 8/13 to resolve differences between cancer data provided in your July 9, 2014, response to FDA's June 10, 2014, Information Request (IR) and your briefing document for the Endocrinologic and Metabolic Drugs Advisory Committee meeting on liraglutide for obesity.

- 1. The T2DM pools in the two documents include the same number of patients and cumulative follow-up time among patients exposed to liraglutide but the pools in the two documents differ for control patients. Appendix 1, Table 3 (T2DM pool) of your response to the IR includes (b) (4) comparator patients (males + females) and (b) (4) patient-years of follow-up. Your briefing document (p.179 and other instances) lists 3,671 comparator patients with 2,525.3 patient-years of follow-up in the T2DM pool.**
- 2. We detected different event counts in the T2DM pool between the 2 documents:**
 - a. Your response to the IR includes (b) (4) events of malignant and unspecified breast neoplasms (excl. in situ) among women exposed to liraglutide in the T2DM pool (Appendix 1, Table 22), while only 7 were reported in the briefing document (p.177).**
 - b. In the briefing document, 3 cases of colorectal neoplasm were reported in comparator patients (p.187) vs. (b) (4) patients in the response to the IR (Appendix 1, Table 37).**
- 3. Please explain the above mentioned discrepancies.**

Thanks for your help. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/12/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 Saxenda (liraglutide for obesity)
Date: Monday, August 04, 2014 12:23:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following comments and requests for information.

- 1. Regarding PHQ9 scores for patient 486024 in trial 1839, please explain why** (b) (4)

- 2. We note that patients 206005 and 206006 in trial 1923 both had WBC of 1100/uL and related adverse events on 5 Oct 09. WBC values on other dates were not low. Please submit any additional information available.**

Thanks for your help. Please confirm receipt of this email.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/04/2014

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
07/09/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) Request for Information
Date: Tuesday, July 01, 2014 1:08:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following comments and requests for information.

(b) (4) are impurities in the liraglutide drug product

Based on results from studies evaluating leachables from the container closure system, storing the drug product for (b) (4) months at 2 – 8C followed by (b) (4) days at 30C may result in human exposure to (b) (4) mcg/day (b) (4) (combined), an exposure that (b) (4) the threshold of toxicological concern (TTC).

- 1. Please provide information on the time dependency of the formation of (b) (4) in the drug product stored at room temperature.**
- 2. Please provide a tabulated summary of all genotoxicity data for (b) (4) establishing that it is not genotoxic.**
- 3. Please provide your justification for the proposed specifications for (b) (4) in the drug product.**

Thanks for your help. Please confirm receipt of this email.

Sincerely;
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
07/01/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - Request for Information
Date: Tuesday, June 24, 2014 12:03:00 PM
Attachments: [24June14_liraglutide_Information_request.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

- **Please respond to the requests contained in the attached PDF document.**

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Information request for sponsor of NDA 206321 (obesity):

We are reviewing (b) (4) you have included in your proposed labeling (b) (4)

Based on our initial review, we have the following concerns:

(b) (4)

(b) (4), please provide the following information for our review:

(b) (4)

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/s/

PATRICIA J MADARA
06/24/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - Request for Information
Date: Friday, June 20, 2014 3:24:00 PM
Attachments: [20June14 Liraglutide Information Request.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

- **Please respond to the requests contained in the attached PDF document.**

You may respond unofficially, via email, but also submit the information officially to your NDA. Note we are requesting submission of the information by June 27, 2014.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please provide the following information by June 27, 2014. Contact us immediately if clarification is needed.

1. Provide sex-, age-, and exposure specific person time of follow-up (intent-to-treat) for each of the following clinical trial pools. Refer to Table 1 for specific age categories and provide one such table for each study pool.

Study pools:

- a. Pool 1: obesity trials (Saxenda): Phase-2 and Phase-3 trials, including extension and observational follow-up periods (120 day safety update)
 - b. Pool 2: diabetes trials (Victoza): Phase-2 and Phase-3 trials, including extension and observational follow-up periods
 - c. Pool 3: combination of Pools 1 and 2
2. Provide age-, sex-, and exposure specific counts of all malignant neoplasms (by individual type of cancer and combined) observed in each of the study pools mentioned above. For breast cancer, provide separate counts of invasive cancers, in situ cancers, and combined counts.
 3. Provide separately for each of the studies included in Pool 3 data for the cells listed in Table 2, that is, study-, sex-, and exposure specific patient counts, person-time, and counts of malignant neoplasm by individual type of cancer and combined.
 4. Comment on the appropriateness of the aforementioned study pools in assessing the incidence of malignant neoplasms in the liraglutide development program. Please comment on whether person-time of follow-up is selected to include all malignant neoplasms that were diagnosed during that time and have been adjudicated (Pool 1). In addition, comment on the validity of categorization of malignancy in Pool 2 (diabetes trials), in the absence of adjudication of potential cases.

Table 1. Dummy table for age-, sex-, and exposure specific person-time

Baseline age category	Liraglutide, males		Liraglutide, females		Comparator, males		Comparator, females	
	Number of subjects	Person-years	Number of subjects	Person-years	Number of subjects	Person-years	Number of subjects	Person-years
<25								
25-29								
30-34								
35-39								
40-44								
45-49								
50-54								
55-59								
60-64								
65-69								
70-74								
75-79								
80-84								
85+								
sum								

Table 2. Dummy table, study-specific information on malignant neoplasms

Study number	Liraglutide, males		Liraglutide, females		Comparator, males		Comparator, females	
	Number of subjects	Person-years	Number of subjects	Person-years	Number of subjects	Person-years	Number of subjects	Person-years
1								
2								
3								
...								

Table 2, continued (A, B, ... refers to cancer type)

Study number	Liraglutide, males			Liraglutide, females			Comparator, males			Comparator, females		
	Count, neoplasm A	Count, neoplasm B	Count, neoplasm ...	Count, neoplasm A	Count, neoplasm B	Count, neoplasm ...	Count, neoplasm A	Count, neoplasm B	Count, neoplasm ...	Count, neoplasm A	Count, neoplasm B	Count, neoplasm ...
1												
2												
3												
...												

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/s/

PATRICIA J MADARA
06/20/2014

From: Madara, Patricia
To: "[MTHO \(Michelle Thompson\)](#)"
Subject: RE: NDA 206321 (liraglutide for obesity) - Clarification
Date: Wednesday, June 11, 2014 6:34:00 PM
Importance: High

Hi Michelle;

The team reviewed your proposals and have responded with the following comments:

- **We agree with your proposal. We understand that you will need to generate 134 outputs to address the IR. However, some of the outputs are interrelated and we recommend that you submit responses to the complete IR in 15 business days, i.e., July 3, 2014.**

Please contact me if you have any questions. Please confirm receipt.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]
Sent: Wednesday, June 11, 2014 12:29 PM
To: Madara, Patricia
Subject: RE: NDA 206321 (liraglutide for obesity) - Clarification

Hi Pat,

I am attaching a document from the team requesting additional clarification from the reviewers. Please note, as we are proposing to provide 134 outputs in response to the request, we will need additional time to generate the responses. Therefore, we propose the following: once we receive Division feedback, Novo Nordisk will deliver the response to IR#1, 2, 3 in **15** business days and IR #4 in **20** business days. We would greatly appreciate your timely response to our proposal. Thanks and as always, your help is much appreciated.

Michelle

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Wednesday, June 11, 2014 10:42 AM
To: MTHO (Michelle Thompson)
Subject: RE: NDA 206321 (liraglutide for obesity) - Clarification

Thanks, Michelle;

I will relay any requests for clarification you team has. p

From: MTHO (Michelle Thompson) [<mailto:mtho@novonordisk.com>]
Sent: Wednesday, June 11, 2014 6:44 AM
To: Madara, Patricia
Subject: RE: NDA 206321 (liraglutide for obesity) - Clarification

Thanks Pat, we took an initial look at the request you sent earlier and some things were not clear. This will help, but we may need to come back to you for additional clarifications from the reviewer. I will let you know.

Michelle

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Tuesday, June 10, 2014 11:10 PM
To: MTHO (Michelle Thompson)
Subject: RE: NDA 206321 (liraglutide for obesity) - Clarification
Importance: High

Hi Michelle;

The review team realized that they did not specify the trials to include in the analyses we requested earlier today. Please use the following studies:

1. Phase 2 study 1807
2. Phase 3 study 1839
3. Phase 3 study 1922

Thanks for your help.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Madara, Patricia
Sent: Tuesday, June 10, 2014 4:19 PM
To: MTHO (Michelle Thompson) (mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) Another request for Information
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions contained in the attached PDF document. In addition, please note the requested timeline for response.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Request for Clarification on FDA Request Dated 10 June 2014

Liraglutide 3 mg for Weight Management

Author

Novo Nordisk

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/s/

PATRICIA J MADARA
06/11/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) Another request for Information
Date: Tuesday, June 10, 2014 4:18:00 PM
Attachments: [10June14 IR for Liraglutide NDA 206321.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions contained in the attached PDF document. In addition, please note the requested timeline for response.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

IR for Liraglutide NDA

Please conduct the following analyses. The analyses #1, 3 and 4 should be conducted separately for the three phase 3 studies and also by pooling all the three phase 3 studies. For safety analyses, a separate analysis should be conducted for (1) all grades and (2) moderate to severe grades.

Please submit the response to IR #1, 2 and 3 in 7 business days. If any of these analyses is already submitted, please direct us to its location. Submit the response to IR#4 in 10 business days. Along with the report, please also submit the datasets and analysis codes used for the analysis.

1. Exposure-response for nausea and vomiting. Please conduct both logistic regression analysis and time to event analysis (Kaplan Meier and cox proportional hazard analysis) for these safety endpoints. Both univariate and multivariate analysis (adjusting for known baseline risk factors) should be conducted.
2. Exposure-response for hypoglycemia (focusing on Study 1922)
3. Characterization of efficacy and safety by baseline body weight for both treatment and placebo arms :
 - a. Characterize the above adverse events (nausea, vomiting, and hypoglycemia) by body weight categories.
 - b. Efficacy analysis for both end points (% change from baseline in body weight and proportion of patients with at least 5% weight loss) by body weight categories.
4. Compare the adverse event profiles of patients by weight loss in both treatment and placebo arm. In particular, address the adverse events profile for patients who experience significant weight loss during treatment with liraglutide and compare to other groups within the liraglutide treatment arm. For instance, you can divide the patients into four groups by their weight loss and compare the patients in the highest quartile (patients with highest weight loss) to patients in the other three quartiles. Also, investigate if the adverse events are time dependent particularly for those patients who experience significant weight loss i.e. do these patients exhibit higher rate of adverse events later in their therapy since exposures of these patients will increase over time.

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/s/

PATRICIA J MADARA
06/10/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) Request for Information
Date: Monday, June 09, 2014 10:55:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following comments and requests for information.

- 1. In trial 1839 the primary analysis did not include values from visit 17x for subjects that discontinued from the study prior to visit 17. However, not considering these subjects, it appears that several subjects had a fasting bodyweight measurement after the measurement that was included in the primary analysis. See the listing below for a subset of these subjects. The variables fvstdu and trlday are the fasting bodyweight value and trial day, respectively, for visit 17 (visitnum = 170) taken from the analysis dataset snfb.xpt. The variables vsstresn and vsdy are the fasting bodyweight value and trial day, respectively, for visit 17 (visitnum = 170) taken from the SDTM dataset vs.xpt.**
- 2. We are unable to identify in the protocol why the later measurements were not used in the primary since they were not from visit 17x (vistnum = 175 in vs.xpt). Please clarify why the later measurements were not used in the primary analysis, and if documented in the protocol, provide the section number. Please respond to this request by 6/16/2014.**

(b) (4)



Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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PATRICIA J MADARA
06/09/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 - Request for Information - REMS
Date: Monday, June 02, 2014 10:59:00 AM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following comments and requests for information.

- **Your NDA submitted on December 20, 2013, included a Risk Evaluation and Mitigation Strategy (REMS) consisting of a communication plan. FDA and Novo Nordisk are in the process of modifying the Victoza REMS. Once the Victoza REMS modification is approved, we request that you revise the REMS submitted for NDA 206321 to include all elements and revisions made to the Victoza REMS that are applicable to the Saxenda REMS.**

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
06/02/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - request for information
Date: Tuesday, May 20, 2014 1:16:00 PM
Attachments: [20May14_stats_info_request.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions and comments contained in the attached PDF document.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

For trial 1839 we are unable to replicate the subject disposition presented in Table 10-1 of the CSR. As can be seen below using the analysis dataset s.xpt, we are unable to match the number of discontinuations due to *Withdrawal Criteria* (210 vs. 555) and *Other* (486 vs. 141). However, when we used the analysis dataset scf.xpt we were able to get similar but not identical results on *Withdrawal Criteria*. Note also that the individual components of the *Withdrawal Criteria* in Table 10-1 for the placebo group do not add up to the overall total (262 vs. 261).

We have the following requests:

- For trial 1839, please confirm whether the information in Table 10-1 is correct.
- For trial 1839, please clarify why disposition numbers from the s.xpt analysis dataset (based on the output below) are different from the numbers in the CSR. Note that for trial 1922 there is no difference between the disposition table in the CSR and counts from the s.xpt analysis dataset.
- For trials 1839, 1922, 3970, 1923 and 1807 please provide the program code for the primary disposition table.

Please submit responses and the requested material by May 27, 2014.



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PATRICIA J MADARA
05/20/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - Request for Information
Date: Friday, May 16, 2014 4:40:00 PM
Attachments: [16May14 clinical information requests.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions contained in the attached PDF document.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We noted the following statement in the footnote of Table 1 [laboratory values for patient 490007] in the 29 Apr 2014 submission (response to FDA request):

Note the ALT value at week 4 was not included in the original table in the Clinical Trial Report due to the values that were used in the programming for impossible values (for ALT set to 0 to 1500). As this ALT value was outside this range an error code flag was generated and the value was mistakenly omitted from the listing.

Questions and requests:

- What were the upper and lower thresholds used to define “impossible” values for each clinical laboratory test and vital sign abnormality?
- Aside from this ALT value for patient 490007, list other laboratory tests/vital sign abnormalities and individual values that were excluded from the clinical trial reports because they were above or below these thresholds.
- Recalculate any laboratory/vital sign analyses that excluded these values.

In addition, please provide the following:

- Provide a brief narrative for each patient in the trials with ALT values > 10x ULN.
- Patient 152024 from trial 1807 has some very abnormal laboratory (particularly hematology) laboratory values on 13 Aug 2007. There were no adverse events associated with these values. Were these values flagged at all by the investigator or the medical monitor? Were they considered laboratory error?
- The laboratory analyses that you have provided in the ISS do not provide information about the proportion of patients in each treatment group with markedly high outliers at any point during the trial. For example, we requested the following in the information request dated 12 May 2014 for the diabetes trials:
 - ALT: > 3x ULN, > 5x ULN, > 10x ULN, and > 20x ULN
 - AST: > 3x ULN, > 5x ULN, > 10x ULN, and > 20x ULN

Provide these analyses for the weight management trials (proportion per treatment group), in addition to the following other outlier analyses:

- Alkaline phosphatase > 2.5x ULN, > 5x ULN, > 20x ULN
- Total bilirubin: > 1.5x ULN, > 3x ULN, > 10x ULN
- CK: > 5x ULN, > 10x ULN
- Serum creatinine: > 1.5x baseline, > 3x ULN, > 6x ULN
- Hemoglobin: < 8 g/dL; > 2 gm/dL above ULN, > 4 gm/dL above ULN
- WBC count: < 3000/mm³, < 2000/mm³, < 1000/mm³
- Neutrophil count: < 1500/mm³, < 1000/mm³, < 500/mm³
- Lymphocyte count: < 800/mm³, < 500/mm³, < 200/mm³; > 4000/mm³, > 20000/mm³

- Platelet count: $< 75000/\text{mm}^3$, $< 50000/\text{mm}^3$, $< 25000/\text{mm}^3$
- Corrected serum calcium: $> 11.5 \text{ mg/dL}$, $> 12.5 \text{ mg/dL}$, $> 13.5 \text{ mg/dL}$; $< 7 \text{ mg/dL}$, $< 6 \text{ mg/dL}$
- Serum glucose: $< 55 \text{ mg/dL}$, $< 40 \text{ mg/dL}$
- Potassium: $> 6 \text{ mmol/L}$, $> 7 \text{ mmol/L}$; $< 3 \text{ mmol/L}$, $< 2.5 \text{ mmol/L}$
- Sodium: $> 150 \text{ mmol/L}$, $> 160 \text{ mmol/L}$; $< 130 \text{ mmol/L}$, $< 120 \text{ mmol/L}$
- Albumin: $< 3 \text{ g/dL}$, $< 2 \text{ g/dL}$

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PATRICIA J MADARA
05/16/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide injection) for obesity
Date: Monday, May 12, 2014 11:41:00 AM
Attachments: [12May14 clinical + stats info requests.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions contained in the attached PDF document.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Clinical Information Requests

1. Do you know how many patients in each treatment group had colonoscopies during the trial? Mammograms?
2. We acknowledge your response to FDA's request dated 10 Apr 2014, table 3-5 regarding reports of deaths in the diabetes trials (IR dated 17 Mar 2014). However, it appears that this listing does not include patient 698004 (trial 1697), who died of renal cell carcinoma. Please clarify the discrepancy and whether the summary (lira vs. comparator) needs to be updated to include this case.
3. We note a discrepancy in ISS table 2-77 vs. 120d safety update appendix 7.1 table 20: it appears that there was one event removed from the malignant thyroid event listing in the updated table; please clarify.
4. Regarding ISS appendix 7.2 table 181, provide the patient-years of exposure that were used to calculate the event rates.
5. Which dataset(s) was (were) used to develop ISS table 2-105 (anti-liraglutide antibodies)? What is the difference between line listings 57 and 58 (appendix 7.9)?
6. For the diabetes pool: provide a 'Hy's law' analysis, as well as categorical analyses of ALT > 3x ULN, > 5x ULN, > 10x ULN, and > 20x ULN and AST > 3x ULN, > 5x ULN, > 10x ULN, and > 20x ULN
7. Provide individual patient IDs associated with the following figures: ISS, Appendix 7.2, Figure 185 and ISS, Appendix 7.2, Figure 256
8. We acknowledge the following statement from your submission dated 02 May 2014: *During preparation of this response Novo Nordisk realized that the datasets provided in the NDA for trial NN8022-1807 were for the full 104 week trial period. Therefore, with the dataset provided in the NDA the Agency would not be able to completely reproduce tables from the 20 week or 52 week interim analyses of NN8022-1807. This is due to the fact that the database was continually updated up through 104 weeks and was not locked at the 20 week or 52 week periods. The CTR's for 20 week and 52 weeks were based on intermediate transfers from the live database and frozen in the statistical production environment.*

This explanation does not make clear why the weeks 20 and 52 data would change. We note in the 1807 study synopsis the dates for the 20-week main period (10 January 2007 to 13 September 2007), the 52-week period (10 January 2007 to 23 April 2008), and the 104-week period (10 January 2007 to 30 April 2009) were all completed well before the NDA was submitted. Please clarify.

Stats Information Requests

1. In trials 1923, 1922, and 1839, subjects that withdrew from the study were asked to come in for a measurement at the nominal time-point of their 56 week visit. For each trial please provide the variable (and dataset) name which identifies these subjects. If such a variable does not exist, please provide the program code used to identify these subjects.

-
2. The multiple imputation strategy imputed missing values after withdrawal based on how similar subjects in the placebo arm that continued in the study. For each trial please provide the program code for these analyses.

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/s/

PATRICIA J MADARA
05/12/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - request for information
Date: Friday, April 25, 2014 2:12:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have the following request for information.

- **Please submit the statistical programs for the primary analysis of co-primary endpoints in trials 1839, 1922, 3970, 1923, and 1807. For each trial we also request that you confirm whether the program code, when applied to the analysis datasets included in the NDA submission, will not need additional modification. For instance a variable referenced in your code may have a different name in the analysis dataset submitted to FDA. Please provide a listing of the modifications that will need to be made, if any exist.**

Please provide the requested material by 5/1/2014.

You may respond unofficially, via email, but also submit the information officially to your NDA.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
04/25/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) Request for Information
Date: Friday, April 11, 2014 2:00:00 PM
Attachments: [11April14 information requests.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide injection for obesity.

We continue to review your application and have additional information requests.

Please respond to the questions contained in the attached PDF document.

You may submit the information informally, via email but also submit it to your application.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

1. Data questions

We are having difficulty reproducing your safety tables based on the datasets provided. For example:

- ALT data as presented in the ISS Appendix 7.5, Table 5
- Supplementary pool II adverse event counts in the Supplementary AE Report Appendix 1, Table 12
- Adverse event counts in trial 1807 Clinical Trial Report, Table 12-2

More generally,

- How does one determine which laboratory data are counted in the main treatment period analyses for the various pools and the individual trials?
- How does one determine which AEs in the sae.xpt dataset are counted in the main treatment period analyses?
 - For the various pools and the individual trials
 - Specifically for trial 1807, how does one determine which treatment emergent AEs are counted in the 52 wk (interim) analysis? Which treatment arm variable is used for this analysis?

Describe what “Control Assessment” refers to in the variable ASSMTP.

2. Clinical questions

- We acknowledge your response (dated 02 Apr 2014) to question 3 in the day 74 letter request. However, we remain curious about patient 490007 in trial 1839, the patient’s reported adverse events and reason for discontinuation (nausea and vomiting), and an apparently unacknowledged ALT value of 1523 at wk 4. As you note at the top of the eCRF for laboratory samples, clinically significant values should be evaluated and reported as an adverse event. Was this value not identified as clinically significant? Did the sponsor audit laboratory values to ensure that clinically significant values were reported as AEs and/or to determine the appropriateness of a “not clinically significant” determination? Do you have any further information regarding this case (e.g., was a hepatitis work-up done)?
- Patient 439014 (death during 1839-ext) was not included in the ISS appendix 7.9 tables 2 and 3 (included EAC diagnoses and comments for deaths). Describe where this information is located in the NDA, or provide the EAC information for this patient.

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/s/

PATRICIA J MADARA
04/11/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206321

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novo Nordisk Inc.
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Robert B. Clark,
Vice President, Regulatory Affairs

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received December 20, 2013, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Liraglutide Injection, 6 mg/ml.

We also refer to your January 10, 2014, correspondence, received January 10, 2014, requesting review of your proposed proprietary name, Saxenda. We have completed our review of the proposed proprietary name, Saxenda and have concluded that it is acceptable. Although we find the name acceptable, we note that this naming approach carries some risk of medication errors due to the overlap in patient population between Victoza and Saxenda, which may lead to therapy duplication if both products are prescribed in error to the same patient. To help reduce the potential for duplicate therapy errors with this naming approach, we agree with pursuing the labeling and outreach measures outlined in your submission, particularly warning against the concurrent use of Victoza and Saxenda.

If **any** of the proposed product characteristics as stated in your January 10, 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 Terrolyn Thomas, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Patricia Madara, Senior Regulatory Project Manager, in the Office of New Drugs at (301)796-1249.

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

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/03/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) - Request for Information
Date: Wednesday, March 19, 2014 3:48:00 PM
Importance: High

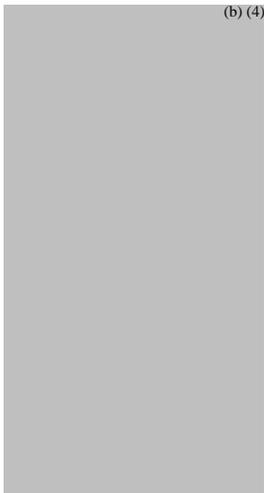
NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide injection for obesity. We continue to review your application and have the following requests for information.

- 1. Provide a definition (one to two sentence description) for each of the following variables.**



- 2. Describe which treatment arm variable was used for the adverse event, safety laboratory, and vital sign analyses in the weight management pool and supplementary pools I and II.**

You may submit the information informally, via email but also submit it to your application.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
03/24/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: Pending NDA 206321 (liraglutide for obesity) - Request for Information
Date: Monday, March 17, 2014 9:32:00 PM
Attachments: [17March14_info_request_Deaths_Supplementary_pool_I.pdf](#)

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide injection for obesity.

We continue to review your application and have the following requests.

1. Please respond to the requests outlined in the attached PDF document.
2. Please provide a timeframe for submission of responses to the information requests issued in our letter dated March 4, 2014.

You may submit the information informally, via email but also submit it to your application.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Information request to sponsor: Please provide the following information regarding deaths from the trials in supplementary pool I.

Supplementary pool I

	Total lira				Comparator total			
Number of patients								
Years of exposure								
	N	(%)	E	R	N	(%)	E	R
Deaths								

Listing of deaths, supplementary pool I

Treatment	Lira dose (if applicable)	Trial	Patient ID	Country	Age (yrs)	Sex	Time on therapy (days)	Cause of death	EAC adjudication

etc...

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/s/

PATRICIA J MADARA
03/18/2014



NDA 206321

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received December 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for liraglutide (rDNA origin) injection, 18 mg/3mL.

We also refer to your amendments dated February 6, 13, and 14, and March 4, 2014.

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 October 20, 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 September 29, 2014.

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

Clinical

1. We acknowledge your submission dated February 14, 2014. Data validity will continue to be a review issue. We request the following information that you offered to provide:

- a. The sensitivity analysis for body weight by excluding the sites with unusual data pattern for body weight
 - b. Information regarding the collection of 100% SDV for partial SDV subjects in trial NN8022-1839
 - c. Ongoing information regarding protocol violations
2. We acknowledge your submission dated February 13, 2014. The adequacy of the safety reporting in the eCRFs will continue to be a review issue. Provide a list of treatment-emergent AEs that were deleted from the CRFs and the reason for each deletion. Some general comments regarding the examples presented:
- a. For example 1 (subject 101018 in trial 1839, “cardiac arrhythmia”), it appears that the patient was feeling ill, so an AE of a pre-existing condition was reported. When it was determined that this was not worsening of the pre-existing condition, the AE was deleted rather than clarification / addition of a new AE (e.g., “feeling ill”). The reason, “changed information” does not adequately explain the rationale.
 - b. For example 2 (subject 508022 in trial 1922, “anxiety”), it appears that the AE was a pre-existing condition, so it was deleted due to “transcription error”. However, it is not clear from the query and reason provided if anxiety could be considered worsened.
 - c. For example 4 (subject 105019 in trial 1923, “anemia”), the description of the events are not clarified by the information in the audit trail. As with other AE deletion reasons, “transcription error” in this case is uninformative.
3. Provide an assessment of patients with laboratory results that are considered clinically significantly abnormal. For example, patient 133039 in trial 1807 (ALT 955 U/L) and patient 490007 in trial 1839 (ALT 1523 U/L). This should be done for all laboratory parameters, with an explanation of how ‘clinically significantly abnormal’ was determined. In addition, a summary of your impression of these cases should be provided, including any work-up conducted.

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.

In addition to the issues listed above, we request that you submit the following information:

Clinical

4. It is noted that the preNDA meeting minutes stated: “An appendix to the NDA, Summary 2.7.4 Summary of Clinical Safety will include hyperlinks to all of the narratives in the submission, according to category (deaths, serious adverse events, withdrawals due to adverse event, and non-serious adverse events of special interest).” However, it does not appear that the narratives were organized according to category. Provide a table of

contents of narratives by category that includes the location in the NDA. Provide narratives for adverse withdrawals for trial 1807, which do not appear to be included.

5. Provide justification with relevant literature for the inclusion of any comparator other than placebo in the CV meta-analysis.
6. Provide missing CRF: Trial 1923, patient 210011 (adverse withdrawal).
7. Provide a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission. If already provided in the NDA, provide the location.

Device

8. It is unclear if subject device (PDS290 Liraglutide 3.0 mg pen-injector) is intended for delivery of a single cartridge, or is intended for long-term, multi-cartridge use. Please clarify this point for us.
9. You marked Biocompatibility as N/A for the subject device (PDS290 Liraglutide 3.0 mg pen-injector) stating that "Only external skin contact during injection". For the pen injector component of the drug, liraglutide, please indicate if the cartridge or the needle that will contact the drug is changed due to the new dose proposed.
10. (b) (4) Please provide a list of all the materials used in the manufacture of all the components of the subject pen injector. The list should include (b) (4) etc., used in the manufacturing of the subject device. In addition, please provide their Material Safety Data Sheets for evaluation.
11. Please submit seven sample pen devices directly to the following address:

Patricia Madara
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3360
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx)*
12. Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - *Current Good Manufacturing Practice Requirements for Combination Products* accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (i.e., Design Controls, Purchasing Controls and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "*Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff*," issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

13. In your response, please provide the name of the facility or facilities that perform the following functions: manufacture the PDS290 and its components; assemble the PDS290; and add the drug substance to the PDS290. Additionally, your response should include the facility that was responsible for developing the PDS290 design specifications, and the facility that maintains the design history file for the combination product. Lastly, please provide the name of the facility or facilities that maintains the records for Design Controls; Corrective and Preventive Action; and Purchasing Controls.

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.

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), Medication Guide and Instructions for Use. 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), Medication Guide, and Instructions for Use 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
03/04/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: Pending NDA 206321 (liraglutide for obesity) - Request for information
Date: Thursday, February 27, 2014 2:12:00 PM
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We continue to review your application and have an urgent request for information.

- 1. For each study covered under the financial disclosure regulations provide:**
 - a. Total number of investigators:**
 - b. Number of investigators who are sponsor employees (full- and part-time):**
 - c. Number of investigators with disclosable financial interests (form FDA 3455):**
 - d. Number of investigators with certification of due diligence (form FDA 3454, box 3):**

You may submit the information informally, via email but also submit it to your application.

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
02/27/2014

From: Madara, Patricia
To: [MTHO \(Michelle Thompson\) \(mtho@novonordisk.com\)](mailto:mtho@novonordisk.com)
Subject: NDA 206321 (liraglutide for obesity) URGENT REQUEST FOR INFORMATION
Date: Tuesday, February 04, 2014 11:40:00 AM
Attachments: [2014-02-04 Liraglutide IR.pdf](#)
Importance: High

NDA 206321

INFORMATION REQUEST

Hi Michelle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for liraglutide for obesity.

We have started to review your application and have an urgent request for information. Please see the attached PDF document for details. Note that we require a response by Thursday, February 6th.

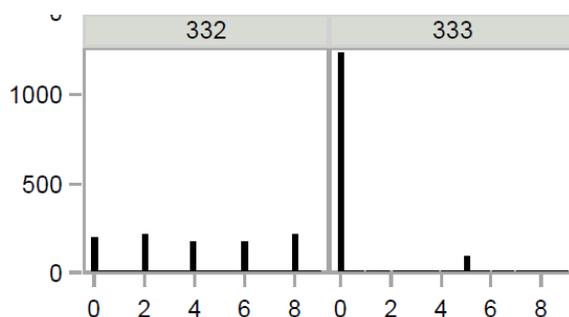
Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We would like to call your attention to a concern that has arisen during our preliminary review of your application in preparation of a filing decision. In an analysis that aimed to look for sites with unusual data patterns of vital signs, we noted that multiple sites stood out as unusual. For example, although the protocol-directed instructions for blood pressure measurement state that the auscultatory method should be used, the measurement must be taken with precision to the nearest 2 mmHg, and at least two measurements at intervals of at least 2 minutes should be performed, we note that there are multiple sites at which the vast majority of recorded systolic and diastolic blood pressures end with the digit '0' or '5.' For example, consider the distribution of the last digit of all SBP values recorded at site 332 compared with site 333:



As a single example of patient-level data at Site 333, consider the blood pressure values recorded for the first subject (NN8022-1839/333001):

VISIT	BP #1	BP #2
VISIT 1 (WEEK -2)	130/90	130/90
VISIT 3 (WEEK 0)	130/90	130/90
VISIT 4 (WEEK 2)	130/90	130/90
VISIT 5 (WEEK 4)	120/70	120/70
VISIT 6 (WEEK 6)	130/80	130/80
VISIT 6C (WEEK 12)	120/80	120/80
VISIT 7 (WEEK 12)	110/80	110/80
VISIT 8 (WEEK 16)	125/80	130/80
etc.

Similar patterns were observed at multiple sites across trials in your development program.

Although blood pressure itself is an important parameter assessed in our safety evaluation, the prevalence of these unusual patterns of recorded blood pressures raises additional concern regarding trial conduct at sites, accuracy of recorded data, and the adequacy of site monitoring. We note that a subject's recorded weight, like blood pressure, requires trust that investigators are recording accurate information on case report forms.

Please provide your response to this concern, including details regarding how you monitored and audited sites in your program, by Thursday, February 6. Alternatively, we are willing to discuss via teleconference this week.

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/s/

PATRICIA J MADARA
02/04/2014



NDA 206321

NDA ACKNOWLEDGMENT

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: liraglutide (rDNA origin) injection; 6mg/ml

Date of Application: December 20, 2013

Date of Receipt: December 20, 2013

Our Reference Number: NDA 206321

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
12/27/2013



IND 073206

MEETING MINUTES

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for liraglutide injection for treatment of obesity.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2013. The purpose of the meeting was to come to agreement with the Agency on the content and format of the NDA for liraglutide for obesity.

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 Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
NovoNordisk handout

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: September 10, 2013 @ 1:30 PM
Meeting Location: White Oak Campus, Building 22, Conference Room: 1315
Application Number: IND 073206
Product Name: liraglutide injection
Indication: as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea
Sponsor/Applicant Name: Novo Nordisk, Inc.
Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Patricia Madara

FDA Attendees

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Jean Marc Guettier, M.D.	Director (acting)
Eric Colman, M.D.	Deputy Director
Amy Egan, M.D., MPH	Deputy Director for Safety
James P. Smith, M.D., M.S.	Clinical Team Leader
Julie Golden, M.D.	Medical Officer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Anthony Parola, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics; Division of Biometrics II

Mark Rothmann, Ph.D.	Team Leader
----------------------	-------------

Bradley W. McEvoy, Ph.D. Statistical Reviewer @ DMEP

Office of Biostatistics; Division of Biometrics VII

Janelle Charles, Ph.D. Statistical Reviewer @ DMEP

Office of Surveillance and Epidemiology (OSE)

Margarita Toss Safety Regulatory Project Manager

**OSE; Office of Medication Error Prevention and Risk Management (OMEPRM)
Division of Medication Error Prevention and Analysis (DMEPA)**

Carol Holquist, R.Ph. Director
Yelena Maslov, Pharm.D. Team Leader

**OSE: Office of Medication Error Prevention and Risk Management (OMEPRM)
Division of Risk Management (DRISK)**

Cynthia LaCivita, Pharm.D. Team Leader

Office of Scientific Investigations; Division of Good Clinical Practice Compliance

Cynthia Kleppinger, M.D. Medical Officer

Center for Devices and Radiological Health (CDRH);

Isabel Tejero

Office of Special Medical Programs; Office of Combination Products

Patricia Y. Love, MD., MBA Deputy Director
Bindi Nikhar, M.D. Senior Clinical Advisor (Acting)

NovoNordisk Attendees

Alan Moses	SVP, Global Chief Medical Officer
Anne Phillips	SVP, Clinical Medical & Regulatory Affairs
Peter Kristensen	SVP, Global Development, R&D
Peter Schelde	CVP, GLP-1 & Obesity
Christine Bjorn Jensen	International Medical Director
Henning Friis Andersen	International Project Statistician
Howard Uderman	SMD, Clinical, Medical & Regulatory Affairs
Lisbeth Vesterg Jacobsen	Sr. Clinical Pharmacology Advisor
Liselotte Bjerre Knudsen	Senior Principal Scientist, Diabetes Pharmacology
Niels C. Nyborg	Non-Clinical Project Director
Trine Brigitte Moulvad	VP Diabetes & Obesity

Robert B. Clark	VP, Regulatory Affairs, Clinical, Medical & Regulatory Affairs
Jim Wang	Senior Director, Global Regulatory Affairs
Stephanie DeChiaro	Senior Manager, Regulatory Affairs, Clinical, Medical & Regulatory Affairs
Michelle Thompson	Senior Director, Regulatory Affairs, Clinical, Medical & Regulatory Affairs

1.0 Background

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) injection, currently approved under NDA 022341 (Victoza) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Novo Nordisk is also developing liraglutide under IND 073206, as a treatment for obesity and weight management. IND 073206 was submitted on September 4, 2008 with three phase 3 protocols. These studies are currently being conducted in support of an obesity indication.

Of note, the currently approved doses for Victoza are 0.6 mg, 1.2 mg, or 1.8 mg once daily as a subcutaneous injection. The company is seeking approval of a 3 mg per day dose for treatment of obesity.

According to the sponsor, the purpose of this meeting is to discuss and come to agreement with the Agency on the content and format of the NDA, the list of submitted questions, and the identification of any issues that could hinder the review process or result in a refuse-to-file action.

2. Discussion

All questions and premeeting responses follow in regular font. Meeting discussion appears in **bolded** font. Meeting discussion / comments follow questions #1, 3, 4, 7, and 17.

2.1. Clinical Questions

Question 1:

Is the proposal for evaluation of dose-response relationship on efficacy endpoints acceptable to the Agency?

FDA Premeeting Response

No. The statistical methods that will be used to evaluate the dose-response relationship need to be described. Moreover, we have concern that the dose-response evaluation for trial 1807 may be confounded since the availability of week 52 data relies on whether the patient consented at week 20 to enroll in the study extension phase.

Meeting Discussion

NovoNordisk (NN, the sponsor, the company) noted they would be specifying the dose comparisons in detail. Regarding the dose-response for trial 1807, they understand the Agency's concerns and will be analyzing dose-response at week 20 and week 52. In addition, the company will measure mean weight loss at week 20 in patients who do and do not consent to continue in the trial to determine if there are any differences. The NDA will also include data from phase 3 trial 1922, which evaluated two doses for 56 weeks. Exposure-response analyses from population pharmacokinetic data from trial 1839 will be submitted as supportive data.

FDA commented that this plan would be a review issue but it appeared to be an acceptable approach.

The Agency asked if the company had conducted any mechanistic modeling related to exposure-response data. The company commented that they had not conducted any modeling.

Question 2:

Can the Agency confirm that efficacy from the 56 weeks exposure along with the evaluation of long term (>56 weeks) exposure is acceptable to support the NDA?

FDA Premeeting Response

We consider the 56-week data from the three Phase 3 trials (1839, 1922, 1923) to be the pivotal data in support of the efficacy of liraglutide for weight management. For the reasons stated in the response to question 1, we have concerns about data from trial 1807 beyond 20 weeks, and this trial will be considered supportive. The acceptability of data from the extension to trial 1839 for further labeling updates will be a review issue, but note that we have concerns regarding the integrity of the trial given that data from the first year will be unblinded and made public while the extension portion of the trial is ongoing.

Question 3:

Does the Agency agree to the proposed methodology to define this criterion and to the analyses that will be provided in the NDA?

FDA Premeeting Response

No. In addition to findings from this analysis being considered exploratory, we have the following comments on the proposed methodology. First, we caution against using last observation carried forward when addressing missing data. For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. Second, we caution using data from trial 1807 due to concerns of confounding (see the response to Question 1). Third, we recommend using positive and negative predictive value to evaluate the "stopping rule." Finally, to aid in the interpretation of the findings, we recommend presenting results separately using liraglutide 3.0 mg data only and all liraglutide dose data combined.

Meeting Discussion

The company noted that they understood the Agency's concerns regarding the use of LOCF to account for missing data. However, this method had been prespecified. They planned to include several other sensitivity analyses to address FDA's concerns.

FDA commented that this should provide helpful information.

NN stated that trial 1807 would be removed from the analysis.

FDA noted that the last column in Table 8 was not actually the positive predictive value. NN commented they were analyzing week 56 responders who also had an early response but had no formal title for this data. They will change the terminology to clarify that they would be using positive and negative predictive value and will also include sensitivity and specificity.

The sponsor asked why FDA wanted submission of data for doses other than the 3 mg dose. In trial 1922, there were 200 subjects dosed with 1.8 mg, representing only about 6% of the total number of subjects.

FDA stated that it would be helpful to see efficacy by dose. However, since 1807 would be removed from the analysis, and the results from 1922 would be provided separately, FDA agreed that an analysis by dose was not needed.

Question 4:

Does the Agency agree with the proposed pools to be submitted in the liraglutide weight management NDA?

FDA Premeeting Response

In general, we support the concept of a weight management pool and supplemental pools for evaluation of safety. In addition to your proposed weight management pool, please provide a second weight management pool of the 56-week data from 1923, 1839, and 1922.

Meeting Discussion

The company asked for clarification as to why the Agency was requesting a separate weight management pool of 56-week data from trials 1923, 1839, and 1922 only. They noted that the five trials were almost identical.

FDA stated that study 3970 provided only 32-week data. In addition, trial 1807 had other limitations, as discussed previously.

FDA stated that NN's proposal was acceptable, but noted that a review of the individual trials would additionally inform our understanding of the safety profile. As the review is ongoing, further analyses may be requested as needed.

Question 5:

Does the Agency agree with the proposed safety database cut-off date (02 July 2013), which allows for inclusion of 1-year double-blind controlled trial results from 4 clinical trials (1807,

1839, 1922, 1923) + 32 weeks results from 1 clinical trial (3970) in the liraglutide weight management program and SAEs and pregnancies from the ongoing trial 1839 extension and trial 3967?

FDA Premeeting Response

We don't have any concerns with the proposed data cut-off.

Question 6:

Does the Agency agree that only SAEs and pregnancies up until DBL (02 July 2013) will be provided for the ongoing extension of trial 1839 and trial 3967 in the liraglutide weight management NDA?

FDA Premeeting Response

Yes.

Question 7:

Does the Agency agree with the overall proposal for presentation of safety data (Primary Pool, Supplementary Adverse Event Pools) and that only data from controlled periods of the clinical trials will be presented for the Primary and Supplementary Adverse Event Pools?

FDA Premeeting Response

Data should be presented for liraglutide by dose and as total liraglutide. Comparators in the supplementary pools should be presented by placebo and active separately, as well as total comparators. We agree that only data from controlled periods of the clinical trials will be presented for the Primary and Supplementary Adverse Event Pools in tabulated form and provided in datasets; however, MESIs that occur in uncontrolled periods should be discussed in the appropriate section of the ISS. Narratives and CRFs that meet the regulatory definition should be provided for events that occur in controlled and uncontrolled periods.

Meeting Discussion

NovoNordisk stated that the key safety data would be presented in the weight management pool, consisting of five phase 2 and phase 3 studies. For this pool, all safety data for placebo and the 3 mg dose would be presented.

For supplemental pool #1, every available trial will be included and the sponsor proposed comparing liraglutide to a combined placebo + active comparator group.

Supplemental pool #2 does not include obesity studies. This will provide data on the adverse event profile for diabetes vs. weight management.

The company had not proposed to present safety data for these pools by dose; however, the Agency would be interested in evaluating whether there is a dose response for certain adverse events.

The sponsor noted they had concerns about presenting the data by dose since some doses were only studied in the type 2 diabetes population and the number of subjects was limited.

For example, the 1.2 mg dose was a much smaller pool and a bias may be created by separating the data.

FDA suggested that the company provide a separate analysis (by dose), for the individual trials studying multiple doses. As noted previously, a review of the individual trials will additionally inform our understanding of the safety profile, in addition to a review of available exposure-response data.

Regarding analysis of the comparators, the sponsor was unsure that separating placebo from active controls would be informative, since many of the patients in the diabetes trials were on background diabetes medications. They also noted that only one diabetes trial was liraglutide vs. placebo, all others were liraglutide vs. active control.

FDA stated that the sponsor's proposal was acceptable. *[Post meeting comment: for the supplemental pool that includes trial 1807, orlistat should not be included in the comparator pool.]*

Regarding FDA's request for information on MESIs during uncontrolled periods, the sponsor noted that there were no uncontrolled periods for the weight management studies.

FDA requested that MESIs in the supplemental pools during uncontrolled periods be made available for review. NN agreed to provide these data.

NovoNordisk summarized the deliverables: they will include safety information by dose for those trials studying multiple doses and will also provide pooled (all doses) data. The ISS will discuss safety data for each dose.

Question 8:

Does the Agency agree with the proposed approach to evaluate the dose-response relationship?

FDA Premeeting Response

You should present the results from the trials separately.

Question 9:

Can the Agency confirm that safety data from the 56 weeks exposure along with the evaluation of long term (>56 weeks) exposure is acceptable to support the NDA?

FDA Premeeting Response

The acceptability will be a review issue. We note that ~3100 patients will be randomized to liraglutide 3.0 mg in the three 56-week Phase 3 trials (and ~1600 to placebo), which is consistent with the draft Weight Management drug guidance. However, we note that information on long-term exposure will likely be limited due to the small sample size. In addition, we have concern about the representativeness of long-term safety data for patients that did complete up to 2 years of treatment with patients that did not complete 2 years of treatment. The degree to which patients did not complete 2 years of treatment will impact our confidence in the findings.

Question 10:

Does the Agency agree with the proposed subgroups for the safety evaluation?

FDA Premeeting Response

Your proposed subgroups are acceptable, although we may request additional analyses be conducted during the review. Note that because response vs. non-response is a post-randomization characteristic, any similarities or differences in treatment effects observed in this analysis will be confounded and difficult to interpret. In addition, although you are free to conduct subgroup analyses based on baseline AST/ALT, we question how informative these results will be, and we will not consider them to inform efficacy or safety across degrees of hepatic *function*. Finally, note that FDA has not made any determinations regarding the utility of the EOSS score in evaluating drugs to treat obesity.

Question 11:

Does the Agency agree with the proposed approach to present medical events of special interest (MESI)?

FDA Premeeting Response

In addition to the MESIs you have proposed, you should conduct analyses on the following:

1. events specifically relevant to increased heart rate
2. an analysis of liraglutide tolerability, particularly evaluating discontinuations and/or dose reductions for GI adverse events
3. injection site reactions (not limited to allergic reactions)
4. an evaluation of device AEs (e.g., “wet” injections)
5. pregnancy

We disagree (b) (4)

Additional comment regarding AEs leading to withdrawal: For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

Question 12:

Does the Agency agree with the proposal for the cardiovascular meta-analysis?

FDA Premeeting Response

As noted in your pre-NDA meeting package, the meta-analysis for adjudicated major adverse cardiovascular events will incorporate feedback previously provided by the FDA. Therefore, the proposal for the cardiovascular meta-analysis appears acceptable.

Question 13:

Does the Agency agree with the proposal for inclusion of CRFs and Narratives?

FDA Premeeting Response

We agree. You should be prepared to supply any additional CRFs upon request.

Question 14:

Does the Agency agree with the inclusion of post-marketing surveillance data in the NDA?

FDA Premeeting Response

We agree.

Question 15:

Does the Agency agree to the proposal for the 4 month safety update?

FDA Premeeting Response

We agree.

2.2. Regulatory / Administrative Questions

Question 16:

Does the Agency agree with the proposed cross reference strategy?

FDA Premeeting Response

This is acceptable. Please ensure that you specify where in NDA 022341 the referenced information can be found.

Question 17:

To minimize patient and prescriber confusion and reduce the risk of medication errors Novo Nordisk intends to launch liraglutide 3.0 for weight management under a different to-be-approved proprietary name and unique delivery system (PDS290 pen-injector) than for the currently approved Victoza. Does the Agency agree to this approach?

FDA Premeeting Response

In order for us to evaluate the dual proprietary name approach further, we request that you submit a detailed assessment of the naming approach that explores different naming options (e.g., dual proprietary name, a root name Victoza and a modifier, etc.).

Based on the information you have provided in the background package regarding the similarities and differences between the devices and product characteristics for diabetes indication vs. obesity indication, we remain concerned that the dual proprietary naming approach carries a risk of duplicate therapy medication error due to overlapping patient population since most type 2 diabetic patients also have a co-morbidity of being overweight or obese. Therefore, the patients that can be prescribed Victoza for diabetes care could also be prescribed liraglutide for weight management under a different proprietary name. For example, a physician may not recognize that the two products contain the same active ingredient, or Victoza may be prescribed by an endocrinologist and liraglutide for obesity may be prescribed by a family physician under a different proprietary name, or vice versa.¹ Continuous duplicate therapy could result in adverse events that may need clinical intervention.

As a result of our preliminary evaluation, we also encourage you to explore a naming approach for the obesity indication that will contain a root name Victoza and an appropriate modifier, as this approach may avoid the risks of duplicate therapy.

Meeting Discussion

NovoNordisk thanked the Agency for their helpful comments. Currently the company was working through all the possibilities. They would try to select a method that would minimize the possibility of medication errors, either by labeling, packaging or both. They plan to submit their proposal and supporting rationale with the NDA.

The company also thanked the Office of Combination Products and Center for Devices and Radiological Health for their helpful comments.

The meeting ended.

Question 18:

Is the planned approach for data format and tabulations, including the datasets and data? definition tables, acceptable to the Agency?

FDA Premeeting Response

Your proposal to submit analysis datasets in legacy format, submitted as SAS transport (XPORT) files along with corresponding data definition files, is acceptable. See response to Question 28 for details about the desired format of the cardiovascular meta-analysis datasets and content of data definition files.

¹ The Institute for Safe Medication Practices. "Revatio=Sildenafil=Viagra". January 2009.

Question 19:

Does the Agency agree with the proposal for patient data listings?

FDA Premeeting Response

We agree.

Question 20:

Does the Agency agree with the proposal for annotated case report forms?

FDA Premeeting Response

We agree.

Question 21:

Does the Agency agree to the plan to seek a waiver in children from birth to less than 6 years of age and a deferral to conduct studies in children ≥ 6 years to < 18 years until safety and efficacy have been established in adults?

FDA Premeeting Response

Your plan is reasonable. Your requests will be evaluated after the NDA is submitted.

Question 22:

Are there changes anticipated to the guidance document that we should be aware of and act upon prior to the filing e.g. requirements for CV documentation or additional and/or different analyses not mentioned above?

FDA Premeeting Response

Not at this time.

Question 23:

Does the Agency agree that certain aspects of “the Program” (mid-cycle meeting, discipline review letters, late-cycle meeting) would further facilitate the review of the liraglutide 3.0 mg for weight management NDA and will therefore provide for multiple interactions (i.e. review meetings and discipline review letters) during review of this NDA?

FDA Premeeting Response

No, we do not agree.

Bioresearch Monitoring (BIMO) Clinical Data

A sample of the Bioresearch Monitoring (BIMO) Clinical Data is provided in m5/datasets/bimo.

Question 24:

Does the Agency have any comments to the enclosed dataset and does the dataset fulfill the requirements set forth in “Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning”?

FDA Premeeting Response

Office of Scientific Investigations (OSI)

In your dataset, you have lumped all endpoints onto one row per site/treatment arm; these need to be provided each separately. We have provided an example (Attachment 1) of what is needed: for each study and investigator site, the summary statistic separately for each primary efficacy endpoint and endpoint type, by treatment arm. You would also include the standard deviation for treatment effect and the related site effect variables for each row in the example.

The NDA number is missing but the assumption is that it will be added to the dataset once NDA number has been given to the application.

Summary Level Clinical Site Data for CDER’s Inspection Planning

The Clinical Site Data Elements Summary listing will include details on the Principal Investigator and site address. Due to the age of some trials, there are investigational sites that no longer exist or sites where the Principal Investigator is deceased. This will be clearly marked in the provided dataset.

Question 25:

Does the Agency have any comments to this approach?

FDA Premeeting Response

Office of Scientific Investigations (OSI)

We do not recommend that these closed investigational sites or sites where the Principal Investigator is deceased be marked within the OSI requested dataset. A separate column or other notation would be acceptable.

Please be reminded that it is very important that our inspectors have phone numbers and email addresses for all sites in anticipation of planning the inspection. For any closed site, the location of the files and the contact person should be provided. If a PI is deceased, please provide all necessary information regarding the holder of the files. Please also include the chain of possession regarding these files.

SDTM and legacy analysis datasets for trial NN8022-1923

A sample of the SDTM and legacy analysis datasets for trial NN8022-1923 is provided in the following locations SDTM: m5\datasets\nn8022-1923\tabulations\sdm and legacy analysis datasets: m5\datasets\nn8022-1923\analysis\legacy\datasets.

Question 26:

Does the Agency have any comments to the format of the enclosed SDTM dataset?

FDA Premeeting Response

We do not have any comments regarding the format; it appears acceptable. On review of your reviewer's guide for the SDTM datasets, we note that you do not plan to submit some information that has been collected on the CRFs. In particular, we request clarification regarding the following:

- 1 You state that the sample collection date will not be submitted in the SV domain for unscheduled assessments but rather used to decide whether the assessment is a re-test or not. Please confirm that the sample collection date for such an assessment would appear elsewhere in the datasets (e.g., in the LB domain for a laboratory sample measured at an unscheduled assessment).
- 2 The annotated case report form suggests that whether a subject was fasting at the time of laboratory assessment was captured as LBFAST (with LSFASSTXT in SUPPLB providing the reason they weren't fasting, if appropriate), but the reviewer's guide states that these data will not be submitted. Please clarify.
- 3 Your Safety Information Form collects data such as relevant laboratory tests, medical history, etc. in the setting of reported adverse events. Please clarify whether these data will be incorporated into the submitted datasets. For example, if a patient were hospitalized for congestive heart failure and had a clinically significant rise in serum transaminases during the hospitalization, would this laboratory abnormality be included in the dataset as an unscheduled assessment?
- 4 The reviewer guide states that the exposure (EX) domain "is created based on information in the protocol and derived exposure records." Please clarify what this means, specifying what data you intend to use to populate any variables intended to describe patient-level drug exposure.

Question 27:

Does the Agency have any comments to the format of the enclosed legacy analysis dataset?

FDA Premeeting Response

The SDTM reviewer's guide states that "derived data marts," and not the SDTM datasets, were used as the source for the analysis datasets, which raises a concern regarding traceability; it is unclear, based on the information and data submitted, whether the SPID variable will be adequate to establish traceability. As stated in the CDER Common Data Standards Issues Document

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>), it is very important that the results presented in clinical study reports be traceable back to the original data elements as they were collected in the case report form and represented in the SDTM datasets. The submitted SDTM data should

support the accompanying analysis data sets and your reports. Please confirm whether you have verified that the SDTM datasets you plan to submit can be used to generate the analysis datasets. Submission of statistical programs that support traceability between the submitted SDTM datasets and the submitted analysis datasets is strongly encouraged.

Furthermore, your sample analysis data definition file does not provide sufficient details about the variables included in your dataset. Please provide detailed data definition files for all datasets submitted with your application. In the data definition files, provide derivation codes for all derived variables, origin of variable, formats, and comments as necessary. See definition files for the SDTM datasets for reference.

Integrated Summary of Safety (ISS)

A sample of the dataset for the ISS is provided in m5\datasets\iss\analysis\legacy\datasets. This dataset includes the information requested in a May 13, 2013 e-mail from Patricia Madara, Regulatory Project Manager.

Question 28:

Does the Agency have any comments to the format of the enclosed dataset?

FDA Premeeting Response

We acknowledge your submission of sample cardiovascular (CV) meta-analysis dataset and corresponding data definition file. To aid in our assessment of the CV risk of your product, we request the NDA includes integrated datasets for the following domains that incorporate information from all trials (from the weight management and type 2 diabetes development programs) that will comprise your CV meta-analysis:

1. **Demographics:** This dataset should contain, at a minimum, demography, analysis population indicators, treatment variables, trial dates (e.g. randomization date, start of treatment date, discontinuation date etc.), and measured baseline subject characteristics (e.g. smoking status, history of CV disease, etc.).
2. **Cardiovascular Event Committee Findings:** This dataset should contain information (including dates) only for any event that triggers a potential event for adjudication and whether the event was positively adjudicated for inclusion in the CV analyses.
3. **Time-to-CV-Event Analysis:** This dataset should contain important demographic, trial and subject identifiers, study dates (randomization dates, first and last treatment dates, end of study date), CV event variables (for the composite endpoints and individual components), censoring and event dates, censoring reason, and other pertinent subgroup information for the planned time-to-CV-event analyses. While your sample dataset appears to be consistent with our preferred structure, we are uncertain how subjects with events will be coded in your submission as such subjects were not included in the sample data set you provided as part of this briefing package. The attached document

(Attachment 2) provides our preference for the content and data structure of the Time-to-CV-Event analysis data set. Note that such a structure is not required and your format may be acceptable; the main concern is that your primary analysis should be reproducible with minimal data manipulations and all pertinent supportive information is contained in the data sets.

Please submit all integrated datasets in SAS transport (.xpt) format.

Your sample data definition file does not provide sufficient details about the variables included in your dataset. For example, it is unclear what the variable “MACTRAC” described as “Treatment, comp. split in act. or pbo.” represents or what is meant by “primary like analysis”. Please provide detailed data definition files for all datasets submitted with your application. In the data definition files, specify the convention used for missing variables. Also, provide derivation codes for all derived variables used in your statistical analyses.

Additional Clinical Comments

These are additional general clinical items that we request be included in the ISS (note this is a standard list, and we acknowledge that you have already addressed some of these items in your briefing document):

1. Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling
2. Exposure-Response Relationships – important exposure-response assessments
3. Less common adverse events (between 0.1% and 1%)
4. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Laboratory Analyses focused on outliers or shifts from normal to abnormal, providing the criteria used to identify outliers.
6. Marked outliers and dropouts for laboratory abnormalities
7. Analysis of vital signs focused on measures of central tendencies
8. Analysis of vital signs focused on outliers or shifts from normal to abnormal
9. Marked outliers for vital signs and dropouts for vital sign abnormalities
10. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

11. For safety analyses that involve evaluations of continuous variables (e.g., laboratory assessments), your methods should clearly state what values were included in each type of analysis (e.g., scheduled assessments, unscheduled assessments, or both).
12. Overview of ECG testing in the development program, including a brief review of the nonclinical results
13. Standard analyses and explorations of ECG data
14. Overdose experience
15. Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
16. Explorations for:
 - a) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment
 - b) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered
 - c) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment
 - d) Drug-demographic interactions
 - e) Drug-disease interactions
17. Drug-drug interactions
 - a) Dosing considerations for important drug-drug interactions
 - b) Special dosing considerations for patients with renal insufficiency and patients with hepatic insufficiency

Additional REMS Comments

Victoza (liraglutide [rDNA origin] injection) is currently approved for the treatment of type 2 diabetes at lower doses than the dose being proposed for use in the treatment of obesity. Victoza was approved with a REMS to ensure that the benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of pancreatitis. Therefore, we encourage you to submit a proposed REMS with your application for liraglutide for obesity. The proposed REMS should consist of a communication plan and a timetable for submission of assessments.

The goals of the REMS should be the same as those approved for Victoza.

The communication plan should consist of:

1. A REMS Letter addressing the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis to be sent within 60 days of product approval and again at 12 and 24 months after product approval. The REMS Letter should be sent to healthcare providers who are likely to prescribe liraglutide for obesity, or have written a prescription for an obesity medical treatment within the prior 12 month period. This includes, but is not limited to, general practitioners, family practitioners, internists, gynecologists, endocrinologists, cardiologists, and nurse practitioners/physician assistants. Subsequent REMS Letters will be sent to healthcare providers who are likely to prescribe liraglutide for obesity (as described above), healthcare providers who have written a prescription for an obesity medical treatment in the prior 12 months, and any healthcare provider who has prescribed liraglutide for obesity within the prior 12 month period. The REMS Letter should be distributed via electronic mail (e-mail) or by US mail. The letter should also be available via a link from the liraglutide for obesity website, through Novo Nordisk's Medical Information Department upon request, and from Novo Nordisk sales and/or medical representatives during initial visits with healthcare providers. A copy of, or a link to, the USPI and Medication Guide should accompany the REMS Letter.

Templates for print and electronic versions of the REMS Letter have previously been sent to you.

In order to further facilitate prescriber training and education, within 60 days of product approval, and again at 12 and 24 months after product approval, Novo Nordisk will send the REMS Letter to the following professional organizations, and will request that the REMS Letter be provided to the members of the professional organizations:

- American Academy of Family Physicians (AAFP)
- American Academy of Nurse Practitioners (AANP)
- American Academy of Physicians Assistants (AAPA)
- American Association of Clinical Endocrinologists (AACE)
- American Association of Diabetic Educators (AADE)
- American Board of Physician Nutrition Specialists (ABPNS)
- American College of Cardiology (ACC)
- American College of Obstetricians and Gynecologists (ACOG)
- American College of Physicians (ACP)
- American College of Preventive Medicine (ACPM)
- American Diabetes Association (ADA)
- American Gastroenterological Association (AGA)
- American Heart Association (AHA)
- American Medical Association (AMA)
- American Osteopathic Association (AOA)
- American Pharmacists Association (APhA)
- American Society for Metabolic and Bariatric Surgery (ASMBS)
- American Society for Preventive Cardiology (ASPC)
- American Society of Bariatric Physicians (ASBP)
- The Endocrine Society (ENDO)
- The Obesity Society (TOS)

2. A REMS Fact Sheet for Prescribers addressing the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis to be distributed by Novo Nordisk's sales and/or medical representatives during initial visits with healthcare providers detailed/visited during the first 12 months after product approval.
3. A REMS Website (e.g., TRADENAME REMS.com) with a prominent REMS-specific link from the liraglutide for obesity website for the duration of the REMS. This link should direct users to the liraglutide for obesity REMS webpage that describes the REMS program and contains only approved REMS materials. The REMS website should be independent of links to the promotional and/or commercial website and any non-REMS materials about the product. Do not include a link from the REMS website page back to the product website. The liraglutide for obesity REMS webpage should also be accessible directly through a search engine.

The REMS website should include downloadable versions of the USPI, Medication Guide, REMS Letter and the REMS Fact Sheet for Prescribers.

4. A timetable for submission of assessments to include assessments at 1 year, 2 years, 3 years, and 7 years from the date of approval of the initial REMS.
5. Carefully consider if mitigating the potential risk of medication errors should be included as a goal of the REMS. Provide a rationale for your decision.

Additional Office of Combination Products and Center for Devices and Radiological Health (CDRH) Comments

A. General Perspective

1. As confirmed in your email of 8/28/2103, the final to-be-marketed (TBM) combination product using the PDS290 pen-injector was not used in the pivotal Phase 3 obesity clinical trials; instead, a modified FlexPen (different from the original Victoza® pen-injector) was used in these trials. PK studies have been performed for the obesity program to bridge to the original Victoza® (diabetes program) biopharm information. However, it appears that the final TBM combination product for the obesity program, i.e., the PDS290 pen-injector, has not been assessed in PK or clinical trials. Also, Human factors validation studies for the PDS290 to assess the user ability to perform critical tasks are pending submission to the NDA. (b) (4)
Therefore, at this time it is not clear if sufficient information will be provided in the NDA to establish the safety and efficacy of the TBM combination product. Since you plan to submit in a few months, we encourage you to include information such as the following to assist in the filing review. If filed, the acceptability of the information will be determined during the NDA review.
 - a) Detailed description, characteristics, and performance validation of the PDS290 pen-injector
 - b) Detailed design differences between Victoza®, the FlexPen injector used in Phase 3, and the PDS290 pen-injector.

- c) Detailed performance, dose accuracy, and data including depth of injection.
- d) If FlexPen modifications occurred during Phase 3, identify the changes and provide number of patients and length of use of the different pens in each study.
- e) Detailed information on design change [REDACTED] (b) (4) and how the changes were validated.
- f) Justify why a [REDACTED] (b) (4) [REDACTED] the PDS290 injector will not result in meaningful changes in PK parameters of liraglutide.

Also, we refer you to the following guidances regarding the type of technical information that may be applicable to the PDS290 injector.

- g) Final - *Guidance for Industry and FDA Staff; Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products* is accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>
- h) Draft - *Guidance for Industry and FDA Staff - Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4* accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>

B. Manufacturing Practice

1. Combination products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>
2. All device constituent associated documents should be located in Section 3.2.P.7 - Container Closure System. These should include information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations.
3. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.
4. Suggestions regarding the types of documents to submit for review can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>
5. To facilitate the review process, include an Application Roadmap, identifying documents addressing 21 CFR part 820 regulations, and the manufacturing of the finished combination product.

3.0 Attachments and Handouts

Handout (one page table) provided by NovoNordisk at the meeting is attached at the end of this document. It provides information related to the company's discussion of question #7.

Additional Important Information

PREA Requirements

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Prescribing Information

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Attachment 1 (cont.)

TRTEFFE			TRTEFFS
-11.2	50	50	12.538326
-12.7	100	100	
2.9	0	0	2.3005099
-8.7	50	50	7.9990338
-6.3	66.7	33.3	6.2711316
-2.6	33.3	0	2.3014471
0.8	0	0	
-6.6	66.7	33.3	9.647716
-5.5	50	0	3.7818265
-11.2	50	50	12.538326
-12.7	100	100	
2.9	0	0	2.3005099
-8.7	50	50	7.9990338
-6.3	66.7	33.3	6.2711316
-2.6	33.3	0	2.3014471
0.8	0	0	
-6.6	66.7	33.3	9.647716
-5.5	50	0	3.7818265
-11.2	50	50	12.538326
-12.7	100	100	
2.9	0	0	2.3005099
-8.7	50	50	7.9990338
-6.3	66.7	33.3	6.2711316
-2.6	33.3	0	2.3014471
0.8	0	0	
-6.6	66.7	33.3	9.647716
-5.5	50	0	3.7818265

Attachment 2

Table 1: Sample Time to Event Data Definition File

Time to Event Analysis Dataset: (dataset name).xpt						
Variable Name	Label	Type	Length	SAS Format	Source dataset	Derivation/Comments
USUBJID	Unique subject ID	Char				
STUDYID	Study ID	Char				
SITEID	Site ID	Char				
SUBJID	Subject ID for the trial	Char				
POPLN	Population	Char				Specify analysis population for example, on-study, on-treatment.
TRTP	Planned treatment	Char				
TRTA	Actual treatment received	Char				
DSETRT	Dose of treatment	Char				Specify dosage of treatment (e.g. 30 mg of drug X once daily)
EXPTRT	Duration of treatment exposure (in days)	Num				
RANDDT	Randomization date	Num				
TRTSDT	Date of first exposure to treatment	Num				
TRTEDT	Date of last exposure to treatment	Num				
LASVSDT	Date of last visit	Num				
LASCNDT	Date of last contact	Num				
AGE	Age (in years)	Num				
RACE	Race	Char				
BMI	Body mass index (in kg/m ²)	Num				
SEX	Sex	Char				
COUNTRY	Country	Char				
SMOKE	Smoking Status	Char				
DIABDUR	Time since diagnosis of diabetes (in years)	Num				
EVT_NAME	CV Event	Char				Specify each CV event that patient experienced (component as well as composite endpoint) and all-cause mortality. For example, "EVT_NAME" may be have values of "MI", "CV_DTH", "STROKE", "MACE"; see sample dataset for more on format of this variable
CNSR	Censor	Num				This variable represents if the patient is censored for the corresponding CV

						event, described previously. Preferred coding scheme: 1=censored, 0=not censored (event occurred)
EVTSTDT	Event Start Date	Num				Specify start date for when patient first becomes at risk for CV event as described in the protocol and could be equivalent to the date of randomization.
EVTEDDT	Event Date	Num				Specify date of the CV event or censor date if patient never has event.
CNSDTDSC	Censor Description					Describe the reason for censoring in case the patient was censored, e.g. "end of trial", "patient withdrawal", etc. or the CV event if the patient was not censored
DAYS	Number of days to event or censoring	Num				

The partial dataset below provides an example of the content requested for the time to CV event analysis dataset for a study of duration 90 days. The example is based on information for one patient, ID=12345, who had an MI on day 40 and dies on day 60, due to non-CV causes. The primary MACE endpoint is a composite of MI, stroke or CV death, and the secondary MACE+ endpoint is a composite of MACE or unstable angina. Patient 12345 is on treatment for 15 days and censored 10 days after treatment discontinuation for the on-treatment analysis (as specified in study protocol).

Table 2: Example of Partial Time to CV Event Dataset for One Patient

USUBJID	POPLN	EVT_NAME	CNSR	DAYS
12345	On study	MI	0	40
12345	On study	Stroke	1	60
12345	On study	CV death	1	60
12345	On study	UA	1	60
12345	On study	MACE	0	40
12345	On study	MACE+	0	40
12345	On study	All-cause death	0	60
12345	On treatment	MI	1	25
12345	On treatment	Stroke	1	25
12345	On treatment	CV death	1	25
12345	On treatment	UA	1	25
12345	On treatment	MACE	1	25
12345	On treatment	MACE+	1	25
12345	On treatment	All-cause death	1	25

1 Page(s) has 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/

ERIC C COLMAN
10/04/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 73,206

Novo Nordisk, Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your Pre-Investigational New Drug Application (PIND) file for liraglutide.

We also refer to the meeting between representatives of your firm and the FDA on March 10, 2008. The purpose of the meeting was to discuss the phase 3 clinical development program for liraglutide.

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

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 10, 2008
TIME: 2:00 PM
LOCATION: White Oak Campus, Bldg 22
APPLICATION: PIND 73,206
DRUG NAME: liraglutide
TYPE OF MEETING: Type B: PreIND / End of Phase 2

MEETING CHAIR: Eric Colman, M.D.

MEETING RECORDER: Patricia Madara

FDA ATTENDEES:

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Director
Eric Colman, M.D.	Deputy Director
Julie Golden, M.D.	Medical Officer
Iffat Chowdhury, M.D.	Medical Officer
Hylton Joffe, M.D.	Clinical Team Leader
Karen Davis Bruno, Ph.D.	Preclinical pharmacology/Toxicology Team Leader
Todd Bourcier, Ph.D.	Preclinical pharmacology/Toxicology Team Leader
Lina Al Juburi, Pharm.D., M.S.	Chief, Project Management Staff
Patricia Madara, M.S.	Regulatory Project Manager

Office of Biometrics; Division of Biostatistics II

Todd Sahlroot, Ph.D.	Deputy Director
Lee Ping Pian, Ph.D.	Statistical Reviewer @ DMEP

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer
Lucan Bi, Ph.D.	Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Novo Nordisk, Inc.

Sandy Cottrell, Ph.D.	Senior Director Therapeutic Area 1, Regulatory Affairs
Berit Edsberg, M.D.	Global Project Director, Development
Mary Ann McElligott, Ph.D.	Associate Vice President, Regulatory Affairs
Finn Mollgaard	Vice President, Regulatory Affairs
MadsFrederik Rasmussen, M.D., Ph.D.	Associate Director, Medical & Science, Development
Rickey Reinhardt, M.D.	Executive Director, Clinical Pharmacology and Research

Marianne Myhre Rottensten
Rene Tabanera y Palacios
Milan Zdravkovic, M.D., Ph.D.
Patty Wilson

Global Regulatory Affairs Project Director
Senior Associate Director, Biostatistics
Corporate Vice President, Development
Manager, Regulatory Affairs

BACKGROUND:

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1), currently being developed under IND 61,040 as a treatment for type 2 diabetes. A new IND (IND 73,206) for an indication of weight management is now being proposed. The diabetes phase 3 program is already complete. Phase 1 and phase 2 studies supporting the obesity indication have been conducted outside of the United States. NovoNordisk is seeking guidance from the Agency regarding interpretation of currently available clinical data supporting a weight loss indication and feedback on their clinical development program.

The sponsor submitted specific questions for discussion. Draft pre-meeting responses from the Division of Metabolism and Endocrinology Products were sent to Novo Nordisk on Friday, March 7, 2008. Upon review, the company determined that the responses to questions 1a and 1b were clear and did not require any additional discussion.

For convenience, the questions and pre-meeting draft responses are repeated below, in normal font. The meeting discussion follows in bold font.

Questions and Discussion

Preclinical - Adequacy of the preclinical data to support development of weight management indication (b) (4)

Question 2:

Upon review of the studies, as tabularly displayed (Section 12.3 and Appendix 1) and more fully described in the Investigator's Brochure, can the Division confirm that these preclinical studies, as described, are adequate, and sufficient, to support development for registration of these additional weight management indication (b) (4)

FDA Pre-meeting Response

Toxicological assessments conducted to support the diabetes indication will be sufficient to support a weight management indication. As communicated previously under the diabetes indication, the division has not received sufficient information to indicate that thyroid tumors observed in the ongoing carcinogenicity studies are of no relevance to human risk. (b) (4)

[Redacted text block]

Meeting Discussion

NovoNordisk (NN) commented that they would revise the Investigator's Brochure (IB) to address the Agency's concerns about thyroid tumors. The sponsor suggested describing the possibility of thyroid tumors as (b) (4)

The Division of Metabolism and Endocrinology Products (DMEP) noted that the significance of the animal tumors in humans was still uncertain. They recommended using the word "uncertain" until mechanistic studies had been submitted and reviewed.

NN agreed to use of this terminology. The IB, informed consent (IC) and all protocols will be revised to reflect this change. These documents will be submitted to DMEP for review. Also, NN noted they would be cross-referencing the diabetes NDA.

Clinical Pharmacology

Question 3a:

Upon review of the current clinical pharmacology program, can the Division comment on the adequacy of this program to support the weight management indication (b) (4)

Question 3b:

Further, can the Division confirm that the strategy for cross-referencing the clinical pharmacology data as described above is adequate?

FDA Response:

Your overall current clinical pharmacology plan seems appropriate in supporting the weight management indication. However, we have the following specific comments on your clinical pharmacology program:

- Your proposed dose (b) (4) mg in weight management indication exceeds the 1.8 mg dose that was evaluated in your thorough QTc study (Trial 1644 under IND 61,040). In general, we recommend that you conduct the thorough QTc study with a suprathreshold dose. If you are not planning on conducting another thorough QTc study at a suprathreshold dose, you should submit your thorough QTc Study report and the dose selection rationale to the Division.
- According to the synopsis of the proposed Phase 3 protocol NN8022-1839, you have planned to collect samples for liraglutide concentrations at (b) (4) to conduct a population PK analysis. However, we believe that the proposed sampling is inadequate for the following reasons:
 - (a) with trough samples alone, one can only characterize CL, and
 - (b) since body weight has an impact on drug disposition (Trial 1327 under IND 61,040), Vd needs to be characterized as well, and will require sampling around Cmax.

Therefore, the Agency recommends that you revise your sampling strategy in your proposed Phase 3 trial accordingly. In addition, we recommend collecting serial (rich) samples in a subset of subjects in your Phase 3 trial in order to characterize liraglutide disposition in the obese population. This will help you conduct a meaningful population analysis. We also recommend that you consider including collection of samples during

the titration phases to characterize dose-concentration relationship in this population.

- Your brief description of the population PK analysis in this context is not sufficient for us to understand your underlying approach to bridge the information between the two populations (or indications). Therefore, please submit your population PK analysis and/or exposure-response analysis plan for a review by the Pharmacometrics group at FDA.

Additional Clinical Pharmacology Comments:

With your NDA submission please submit the following datasets to support any of your population analysis:

- 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 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 predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide, in the summary of the report, a description of the clinical application of modeling results.

Meeting Discussion

NN commented that they would provide the Agency with data and dose selection rationale for the QTc study that had been conducted (Study 1644). They noted that exposures resulting from the 1.8 mg dose in the study (conducted for the diabetes indication) were comparable to those found in obese patients treated with the ^(b)₍₄₎ mg dose. Furthermore, at the dose studied, they did not see any QTc prolongation. They felt that study 1644 supported the weight management indication.

The Agency stated that it would be very hard to make a commitment at this point. It was noted that the firm had previously argued against a dose greater than 1.8 mg. However, there are concerns with this approach. We will need to review the study report. Generally, suprathapeutic doses are required for tQTc studies.

NN agreed to submit the study report for review.

NN noted the Agency's comments regarding their proposed population PK analysis and agreed to revise the sampling strategy. There will be a substudy to look at population PK. It

will include approximately 40 – 60 subjects (20 – 30 on placebo and 20 – 30 actively dosed). In addition, random samples will still be collected.

FDA questioned if there would be enough exposure, since the dose for obesity ((b) (4) mg) was higher than that studied for diabetes (1.8 mg).

NN noted that they had profiles at lower doses (1.2 and 1.8 mg) and felt they had sufficient PK information. The BMIs of the subjects studied may be slightly lower than in obese patients but, given the data gathered so far, they felt a dedicated substudy at the (b) (4) mg dose was the best path to follow.

FDA commented that it would be most important to gather more information around the Cmax for the (b) (4) mg dose. It was recommended that NN submit their population PK plan.

Clinical Efficacy – Initial Indication within Weight Management

Question 3c:

Are the proposed trials and trial designs adequate and sufficient in scope to support the initial indication (see above in this section 7.2.3.2 for specific wording)? Further, does the Division agree to the dose selection (b) (4) mg/day for the weight management indication?

Specifically, we note:

For the weight management indication (b) (4):

- i) Are the NN8022-1839, NN8022-1922 and the NN8022-1923 trial designs and inclusion/exclusion criteria adequate and sufficient in scope to support the initial submission for the weight management indication?
- ii) Are the endpoints acceptable to support the weight management indication presuming appropriate weight loss at one year?

FDA response:

We consider efficacy for a weight management indication to be based on either the mean percent weight loss compared to placebo or the categorical proportion of subjects who lose 5% of body weight as compared to placebo at one year. The placebo-subtracted mean weight loss must be 5 percent at one year to demonstrate efficacy. We therefore recommend you include the 5% categorical endpoint as a co-primary efficacy endpoint in your obesity trials.

We agree that approximately 3000 subjects randomized to liraglutide (b) (4) mg in one-year trials is adequate exposure for a weight management indication. See additional comments below and in response to questions 4 and 5.

With respect to your proposed dose, we agree with your preliminary assessment of the safety and efficacy of liraglutide (b) (4) mg from your phase 2 study. (b) (4)

Please note that any phase 3 program that studies only one dose assumes some risk that this dose will not demonstrate adequate efficacy or safety.

Additional clinical comments:

- As weight is the primary efficacy variable, it should be measured in a consistent fashion at each visit – that is, in the fasting state.
- A representative sample of study subjects should have a baseline and follow-up measurement of body composition by DEXA, or a suitable alternative.
- In your diabetes trial -1922, we believe that a more meaningful stratification of co-administered oral hypoglycemic medications (b) (4) would be one based on the medications' impact on weight; that is, weight neutral, weight gain-promoting, and weight loss-promoting. All possible acceptable combinations should be pre-specified and the groups should be mutually exclusive. We encourage you to consider a revised stratification plan and discuss with the Division. Subjects should also be stratified into treatment groups by baseline HbA1c; e.g., < 8.5% vs. ≥ 8.5%. We generally recommend that subjects with type 2 diabetes who have confirmed fasting glucose > 270 mg/dL be excluded from obesity trials.
- Many overweight patients with type 2 diabetes are using insulin, which promotes weight gain. You should also study liraglutide in this patient population to evaluate whether insulin therapy mitigates or eradicates the weight loss effects of liraglutide.
- Hypoglycemia is listed as a secondary endpoint in your diabetes trial -1922. You should prespecify how hypoglycemia will be defined, captured, and analyzed.
- You are encouraged to continue your subjects in your trials whenever possible, as long as it is safe to do so. Therefore, subjects who develop hyperglycemia in your diabetes trial -1922 may be candidates for glycemic rescue with increasing doses or addition of oral hypoglycemics, rather than withdrawal. Another secondary endpoint could be the proportion of subjects per group who require such rescue. Your proposed glycemic rescue criteria are too liberal. One approach for rescue that has been recommended to companies has been the following:
 - FPG > 270 mg/dL (15 mmol/L) from baseline to Week 6
 - FPG > 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
 - FPG > 200 mg/dL (11.1 mmol/L) or HbA1c > 8.0% from Week 12 to Week 24

You would also need to include FPG and HbA1c rescue criteria from Week 24 through study end, and justify your choice of rescue criteria cutpoints. Additional oral hypoglycemic medication would be added when the glycemic rescue criteria are met. The last set of body weight and glycemic efficacy parameters obtained prior to glycemic rescue therapy should be used for your efficacy analyses, as rescue therapy will confound the measurements of subsequent measurements of these parameters. Subjects who develop type 2 diabetes in your other obesity trials could also be rescued for hyperglycemia according to these criteria.

- (b) (4)

- We commend you on your proposal to bring prematurely discontinued subjects back one year after the randomization date to measure body weight.

Meeting Discussion

Regarding the different doses proposed for diabetes and obesity (1.8 mg for diabetes, (b) (4) mg for obesity), NN felt the two doses were merited due to differences in the dose-response curves for glycemic control and weight management. (b) (4)

DMEP expressed concern over possible marketing of different doses in two patient populations that overlap substantially. In the real world, it seemed inconsistent, and therefore potentially confusing, to treat type 2 diabetics with a maximum dose of 1.8 mg daily when 80 – 90% of these patients are obese.

NN stated that there was no reason to go above 1.8 mg for glycemic control. They noted that the firm was currently conducting a bridging study and would not make a decision until the results from this trial were analyzed.

Regarding the Division’s pre-meeting comments discussing the primary efficacy measurement, NN noted that obtaining body weight in a fasting state at every visit was not feasible. However, subjects would be asked to come in fasting every time they returned for essential lab measurements.

Regarding the Division’s pre-meeting comments discussing the need for body composition measurements, NN noted that they had conducted a phase 2, dose-ranging trial that included DEXA scans and CT scans in a subgroup of patients. They found 75 – 85% of the weight loss was due to fat mass reduction. However, the placebo group was very active and a statistically significant difference between the treatment groups was not achieved. DMEP agreed to review those data prior to making a determination about the necessity of further body composition measurements in phase 3 studies and prior to the sponsor opening the IND.

With respect to the study in patients with type 2 diabetes, NN noted that the FDA’s proposed stratification plan for oral hypoglycemics was a good suggestion. NN proposed (b) (4)

[Redacted text block]

NN will implement glycemic rescue criteria for patients with diabetes. The rescue limits will be as follows:

- Fasting plasma glucose (FPG) > 220 mg/dL at randomization
- FPG > 200 mg/dL from week 24 to week 52
- FPG > 180 mg/dL after one year

The HbA1c rescue cutpoint will remain at 8%.

FDA commented that the stringency of some of these criteria may affect the integrity of the trial if these criteria result in many discontinuations and there are substantial dropouts for other reasons (as is typical of trials for anti-obesity agents). FDA acknowledged the ethics of loosening some of the glycemic rescue criteria and recommended that the sponsor reconsider these issues and submit a justification for the new cutpoints if these criteria are modified.

(b) (4) the Division responded that HbA1c should be used in conjunction with FPG after approximately 12-16 weeks of treatment with study medication, because HbA1c will more accurately reflect overall glycemic control after this time period.

(b) (4)

(b) (4) The Division strongly recommended including a 1.8 mg dose arm in this study. Doing so will provide a head-to-head comparison of the 1.8 mg and (b) (4) mg doses with regard to efficacy and safety (e.g., hypoglycemia) in obese patients with diabetes, which is more valid than a comparison of efficacy and safety data across different clinical trials.

DMEP again reiterated concerns about marketing two different doses to overlapping populations. (b) (4)

(b) (4) NN asked how many patients would be required in the diabetes trial for the obesity indication that compared 1.8 mg to (b) (4) mg, and suggested 200 patients on placebo, 200 patients on 1.8 mg and 200 patients on (b) (4) mg. The Division stated that these sample sizes were reasonable for this trial. One concern is that many patients will be given the (b) (4) mg dose to treat both obesity and diabetes, if liraglutide is approved for both indications. However, the entire diabetes program will establish efficacy and safety for glycemic control with at most the 1.8 mg dose. (b) (4)

(b) (4)

(b) (4)

(b) (4)

With respect to the Division's comment regarding hypoglycemia, NN asked the Division for clarification. DMEP stated that hypoglycemia should be predefined in all clinical trials so that hypoglycemia events are captured in a standard way. NN was referred to the following publication: **Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005 May; 28(5): 1245-9.**

Meeting Discussion

NN asked for more insight regarding the proposed extension to trial 1839



FDA response: See the response to question 3d.

Clinical Safety

Question 4:

Can the Division confirm the adequacy of the overall safety monitoring strategy in the proposed phase 3 studies and specifically the proposed special safety monitoring strategy in the proposed phase 3 studies?

FDA response:

The standard safety monitoring strategy appears appropriate. You should specifically monitor for changes in heart rate as well as injection site reactions. Please clarify what the thyroid examinations in the phase 3 trials will include.

With respect to your hypoglycemia monitoring proposal, all subjects on oral hypoglycemics or those who start them during the course of the trials should monitor blood glucose at home.

We do not agree with your plans [redacted] (b) (4)



[redacted] This issue will require further discussion. Please clarify at the end-of-phase 2 meeting how you will be assessing in the phase 3 program whether liraglutide is associated with thyroid neoplasms in humans.

Meeting Discussion

NN agreed to conduct physical exams of the thyroid at baseline and measurement of calcitonin every 12 weeks (which is a change from procedures described in the briefing document). They noted that exposures comparable to those in the diabetes program would be generated and they would follow the same approach: An internal safety review committee would be set up to identify any individuals with calcitonin levels greater than 2 times the upper limit of normal. These subjects would be referred for follow-up. They noted that physical exams at screening would detect gross changes only and were not useful in assessing thyroid carcinoma.

DMEP noted that the results may be consulted to specialists within and outside of FDA.

(b) (4)

The Agency cannot dismiss the animal data. The DMEP preclinical pharmacology review team commented that animal studies have shown a multispecies signal for C cell tumors and hyperplasia at clinically relevant exposures. DMEP stated that NN should submit final study reports on the mechanistic data to permit thorough review.

Pancreatitis has been associated with Byetta, another GLP-1 analog. Therefore, you should routinely monitor serum lipase during the phase 3 clinical trials of liraglutide and you should develop a prespecified package of tests that all patients with pancreatitis undergo (e.g., gallbladder ultrasound, serum triglycerides, checklist for other causative medications, etc.). In addition, we recommend that you exclude patients with a history of chronic pancreatitis and patients with a history of idiopathic acute pancreatitis from the phase 3 clinical trials.

Meeting Discussion

NN noted that they would implement FDA recommendations regarding the above exclusion criteria and will monitor amylase and lipase levels in the clinical trials. In addition, similar to calcitonin, a safety committee will be involved and discussions will be held with the investigator. In cases of acute pancreatitis, it should be noted that the study investigator may not be the first individual to diagnose or treat the condition.

The Division questioned the procedure for those study subjects whose pancreatitis was obviously caused by something other than liraglutide. NN commented that their practice up to this point had been not to re-expose the patient to study drug. If the pancreatitis was confirmed to be caused by something else, the Division felt the subject could be restarted on study drug. These data would add useful information to the overall currently limited body of knowledge about the association between pancreatitis and GLP-1 analogs.

With respect to your proposed psychiatric exclusions, we agree with excluding subjects on tricyclic antidepressants or anti-psychotics known to lead to weight increase. However, excess rates of psychiatric adverse events in the higher doses from your phase 2 study were noted, and although we are unaware of a specific mechanism whereby liraglutide would cause psychiatric events, this finding will need to be explored further. We are asking obesity programs studying drugs with a central mechanism of action to administer the Columbia Suicidality Severity Rating Scale (C-

SSRS)¹, the Generalized Anxiety Disorder (GAD)-7², and the Patient Health Questionnaire (PHQ)-9³ in all subjects at each study visit. For safety, we would suggest you consider excluding: subjects with a history of Major Depressive Disorder within the last 2 years; subjects with any lifetime history of a suicide attempt; subjects with a history of any suicidal behavior in the last month; and subjects with a history of other severe psychiatric disorders, e.g., schizophrenia or bipolar disorder.

Meeting Discussion

Regarding psychiatric adverse events, the sponsor commented that they did not believe there were any clear signals for psychiatric findings with liraglutide; the most common psychiatric AE being insomnia. NN will exclude study participants with a past psychiatric history or currently taking anti psychotic drugs.

DMEP noted that liraglutide is presumed to get into the brain and is, therefore, considered to be centrally-acting. Preliminary review of the information NN provided suggested the possibility of a drug effect. If more psychiatric and/or neurological adverse reactions are seen in phase 3 trials and information is not collected prospectively, a retrospective analysis would then become necessary.

NN commented that their main concern was with use of the C-SSRS, which is not validated in the population being studied.

The Division stated that this was an evolving area. FDA is concerned about drug-related depression and all the symptoms associated with it, including suicidality. All the development programs for obesity are being asked to include the same instruments to screen for depression and suicidality, including the C-SSRS. It is in the firm's own best interests to use these tools.

Patient Exposure

Question 5:

Does the Division consider the number of patients and the extent of exposure sufficient to grant market authorization for the weight management indication. (b) (4)

(b) (4) *under the precondition that the benefit/risk profile for liraglutide is found favorable?*

FDA response:

A total of 3000 subjects randomized to liraglutide (b) (4) mg in placebo-controlled trials evaluating weight change over one-year is generally an acceptable exposure for a weight management indication, assuming safety and efficacy can be demonstrated. (b) (4)

¹ For further information contact: posnerk@childpsych.columbia.edu

² Spitzer RL, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092-7.

³ Kroenke K, et al. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.

Pediatric development obligations

Question 6: Does the Division have any comments on these plans?

FDA response:

We agree with the plans for waiver of studies in children (b) (4) years and deferral in children ages (b) (4)-17 until data in adults (b) (4). A safety and efficacy study for an obesity indication in the proposed pediatric population should be one year in duration. Eligible patients should have age- and sex-matched BMIs greater than or equal to the 95th percentile. Safety evaluations should include linear growth and other growth-related endpoints, such as Tanner stage. Efficacy will be assessed as change in BMI from baseline to year 1 as compared to placebo. Other details of the study design should be discussed with the Division prior to its initiation.

Meeting Discussion

Additional FDA Safety Analysis and Data Format Comments:

Quantitative Safety Analysis Plan

The Statistical Analysis Plan, which generally addresses statistical issues for efficacy, must include a Quantitative Safety Analysis Plan (QSAP). The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESI's, and quantitative methods for analysis, summary and data presentation. See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>

At a minimum the QSAP should address the following components:

- Study design considerations
- Safety endpoints for Adverse Events of Special Interest (AESI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered
- When unanticipated safety issues are identified the QSAP may be amended

Data Submission

The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

Study Data Tabulation Model (SDTM) Issues

1. Format

The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)

2. Domains

a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.cdisc.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.

- i. (DV) Protocol deviations
- ii. (DA) Drug Accountability
- iii. (PC, PP) Pharmacokinetics
- iv. (MB, MS) Microbiology
- v. (CF) Clinical Findings

b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

- i. Tumor information
- ii. Imaging Data
- iii. Complex Inclusion/Exclusion Criteria

2. Variables

- a. All required variables are to be included.
- b. All expected variables should be included in all SDTM datasets.
- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues:

1. Please specify which ADaM datasets you intend to submit.
2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Please indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items: Controlled terminology issues

- a. Please use a single version of MedDRA for a submission. This does not have to be most recent version.
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Please refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed.

Sponsor Meeting Question

At the meeting, NN proposed that all clinical trial reports would be finalized based on the MedDRA dictionary in effect at that time, however, all data would be reconciled to a single common MedDRA dictionary for the ISS. They asked if this would be acceptable to the Agency. DMEP responded that the appropriate Division would be consulted and an answer included in the post meeting minutes.

Post-Meeting Comment

Reconciling to a single MedDRA dictionary version for the ISS is acceptable and recommended. NovoNordisk should describe the procedure used for reconciling and specify which version was used.

ATTACHMENTS: NovoNordisk Handouts

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications

Sponsor Name

Drug Name

IND 73206

NOVO NORDISK

LIRAGLUTIDE (NN2211)

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

/s/

PATRICIA J MADARA

04/03/2008