

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-341**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

22-341

NAME OF APPLICANT / NDA HOLDER

Novo Nordisk Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Victoza (proposed trade name)

ACTIVE INGREDIENT(S)

liraglutide

STRENGTH(S)

6.0 mg/ml

DOSAGE FORM

subcutaneous injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

6,268,343

b. Issue Date of Patent

7/31/2001

c. Expiration Date of Patent

8/22/2017

d. Name of Patent Owner

Novo Nordisk A/S

Address (of Patent Owner)

Novo Alle

City/State

2880 Bagsvaerd Denmark

ZIP Code

FAX Number (if available)

Telephone Number

(454)444-8888

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number(s) (as listed in the patent) 39 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)**

Date Signed  
5/23/2008

**Mary Ann McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, o=US, ou=Novo Nordisk,  
ou=Regulatory Affairs, email=MAMC@NovoNordisk.com  
Date: 2008.05.13 15:25:19 -0400

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Mary Ann McElligott, Ph.D.	
Address 100 College Road West	City/State Princeton/NJ
ZIP Code 08540	Telephone Number (609)987-5831
FAX Number (if available) (609)987-3916	E-Mail Address (if available) mamc@novonordisk.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*



## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 04/30/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE          FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and          Composition) and/or Method of Use</i>			
		NDA NUMBER 22-341	
		NAME OF APPLICANT / NDA HOLDER Novo Nordisk Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Victoza (proposed trade name)			
ACTIVE INGREDIENT(S) liraglutide		STRENGTH(S) 6.0 mg/ml	
DOSAGE FORM subcutaneous injection			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 6,458,924		b. Issue Date of Patent 10/1/2002	c. Expiration Date of Patent 8/22/2017
d. Name of Patent Owner Novo Nordisk A/S		Address (of Patent Owner) Novo Alle	
		City/State 2880 Bagsvaerd Denmark	
		ZIP Code	FAX Number (if available)
		Telephone Number (454)444-8888	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number(s) (as listed in the patent) 19 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed  
5/23/2008

Mary Ann McElligott

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US, o=Novo Nordisk,  
ou=Regulatory Affairs, email=MAMC@NovoNordisk.  
com  
Date: 2008.05.13 15:25:41 -0400

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Mary Ann McElligott, Ph.D.	
Address 100 College Road West	City/State Princeton/NJ
ZIP Code 08540	Telephone Number (609)987-5831
FAX Number (if available) (609)987-3916	E-Mail Address (if available) mamc@novonordisk.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER

22-341

NAME OF APPLICANT / NDA HOLDER

Novo Nordisk Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Victoza (proposed trade name)

ACTIVE INGREDIENT(S)

liraglutide

STRENGTH(S)

6.0 mg/ml

DOSAGE FORM

subcutaneous injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

7,235,627

b. Issue Date of Patent

06/26/2007

c. Expiration Date of Patent

8/22/2017

d. Name of Patent Owner

Novo Nordisk A/S

Address (of Patent Owner)

Novo Alle

City/State

2880 Bagsvaerd Denmark

ZIP Code

FAX Number (if available)

Telephone Number

(454)444-8888

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)



Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed  
5/23/2008

Mary Ann  
McElligott

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US, o=Novo  
Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.05.13 15:28:05 -04'00'

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Mary Ann McElligott, Ph.D.	
Address 100 College Road West	City/State Princeton/NJ
ZIP Code 08540	Telephone Number (609)987-5831
FAX Number (if available) (609)987-3916	E-Mail Address (if available) mamc@novonordisk.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*



## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Dear Review Division:

This template covers both **deferrals and plans** as both must be presented together.

PREA 2007 requires the Pediatric Review Committee (PeRC) to review all waivers and deferrals of required studies in pediatric patients as well as all pediatric assessments and plans prior to approval of an application or supplement.

A Pediatric Plan Must be submitted for all deferred studies. A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics and/or pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation.

We will need:

Draft Approval letter  
Pediatric Page  
Draft Labeling

Please fill out template below, or provide synopsis from Sponsor

## Pediatric Research and Equity Act Deferrals and Plans

For ALL deferred studies, a pediatric plan must also be submitted.

IND/NDA/BLA #:

Product name and active ingredient/dosage form:

Sponsor:

Approved Indication: (NOTE: If the drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

Proposed Indication: (NOTE: If the drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. Age group(s) included in deferral request
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred, partial waiver is being requested)
3. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
  - i. Adult studies completed and ready for approval
  - ii. Additional safety or effectiveness data needed (**describe**)
  - iii. Other (**specify**)

4. Evidence that planned or ongoing studies are proceeding
5. Projected date for the submission of the pediatric assessment (deferral date)
6. Applicant certification

**Pediatric Plan:**

A Pediatric Plan Must be submitted for all deferred studies. A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics and/or pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. The plan should be used as a basis for the PREA requirements.

1. Has a pediatric plan been submitted to the Agency? Note: Pediatric plans MUST be reviewed by the Pediatric Review Committee (PeRC) prior to approval
2. Timeline for the completion of studies
3. Has a Written Request been issued?
4. Please complete as much of the table below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

<b>Study Elements for review</b>
<b>Application # 22-341</b>
<b>Drug Name: Victoza(liraglutide)</b>
<b>Approved Indications: Treatment of type 2 diabetes mellitus</b>
<b>Date Submitted: May 23, 2008</b>
<b>PDUFA DUE DATE: March 23, 2009</b>

**PREA Commitment from draft approval letter:**

**Drug information:**

- **Route of administration:** Subcutaneous Injection

- **Formulation:**

Liraglutide 6.0 mg/ml, 3 ml \_\_\_\_\_ for s.c. injection

Liraglutide placebo, 3 ml \_\_\_\_\_ for s.c. injection

- **Dosage:** Varied, see trial descriptions below
- **Regimen:** once daily injection

**b(4)**

**Types of studies/ Study Design:**

**Two pediatric studies are proposed by the sponsor as follows:**

PK/PD Study: NN2211-1800 "A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Pediatric (10 – 17 years old) and Adult Subjects with Type 2 Diabetes"

**Study Designs:**

**PK/PD Study:** Study 1800 is a sequential 2-part trial involving pediatric and adult subjects with type 2 diabetes.

Part I is a randomized, double-blind, placebo-controlled, 6-week trial in which 18 healthy (or type 2 diabetic – TBD later) pediatric subjects will be randomized either to liraglutide (N = 12) or placebo (N = 6) treatment. Subjects on active liraglutide treatment will receive 0.3 mg liraglutide daily during the first week followed by 0.6 mg in the second week, 0.9 mg in the third week, 1.2 mg in fourth week, 1.8 mg in the fifth week, and 2.4 mg in the sixth and final week, sequentially (subjects on placebo will be given matched placebo treatments each of the 6 weeks). Safety and tolerability will be assessed throughout the 6-week period. A 24-hr PK profile will

**b(4)**

be obtained from each subject at the end (Day 7) of each of Weeks 1, 2, 4, 5 and 6. Dose escalation in Part I will be based on the safety/tolerability at each dose.

Part II is a randomized, double-blind, placebo-controlled, 4-week trial in 18 adults and 18 pediatric subjects with type 2 diabetes. Subjects will be randomized either to liraglutide (N = 12 each for adults and pediatric) or placebo (N = 6 each for adults and pediatric) treatment. Active treatment will constitute escalating weekly doses of liraglutide starting with 0.6 mg (lowest dose) and ending with 2.4 mg (highest dose). Subjects on placebo will receive matched placebo treatment each week. Safety, pharmacokinetics and pharmacodynamics will be assessed throughout the 6-week period.

Note: Based on the safety/tolerability results in Part I, the starting dose in the pediatric population in Part II can either be 0.3 or 0.6 mg. If the starting dose in the pediatric population in Part II is 0.6 mg, the safety/tolerability will be compared to that following the 0.6 mg dose in Part I to decide whether 0.3 or 0.6 mg is the ideal starting dose in the pediatric population.

**Age group and population in which study will be performed:**

**PK/PD Study:** 18 pediatric subjects (age 10-17 years) for part 1 and 18 pediatric and 18 adult subjects for part 2.

**Number of patients to be studied or power of study to be achieved:**

PK/PD study – total of 54 subjects (18 of whom will be adults). See above  
Efficacy and safety trial – total of 160 subjects. See power description under statistics.

b(4)

**Key Inclusion Criteria for the PK/PD Study:**

1. Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject)
2. Male and female pediatric and adult subjects with type 2 diabetes (Part II)
3. Age between 10 – 17 years (both inclusive) for pediatric, and 18 - 45 years (adults)
4. A BMI of > 85<sup>th</sup> percentile for age and gender (pediatric) and  $\leq$  40kg/m (adults)

**Key Exclusion Criteria for the PK/PD Study:**

1. Known or suspected allergy to trial product(s) or related products
2. Type 1 diabetes
3. Use of any anti-diabetic agent other than metformin
4. Female of childbearing potential/breast feeding, intent to become pregnant or not using adequate contraception
5. History of alcoholism or drug abuse
6. Blood donation during the last 8 weeks of the study
7. Receipt of any investigational drug within past 4 weeks of first treatment with study medication

b(4)

**Clinical endpoints:**

**PK/PD Study:**

Standard demographic data will be collected including recording of puberty status (Tanner stages 1-5)

*Safety:*

Laboratory safety (including plasma glucose, hematology, clinical chemistry and urinalysis), physical examination, vital signs, electrocardiogram (ECG) and adverse events will be investigated.

*Pharmacokinetics:*

Plasma concentrations of liraglutide for standard pharmacokinetic analyses will be determined at prespecified timepoints on weeks 1, 2, 4, 5 and 6 for Part I, and all 4 weeks in Part II.

*Pharmacodynamics (Part II only):*

- FPG and insulin will be assessed pre-treatment and following completion of each week of dosing.
- PPG and insulin profiles will be obtained over mealtime during week 4

**b(4)**

**Secondary Endpoints (to be assessed after 14 weeks and 52 weeks of treatment unless otherwise stated)**

- HbA<sub>1c</sub> after 52 weeks
- Percentage of subjects with HbA<sub>1c</sub> < 7.0%
- Percentage of subjects with HbA<sub>1c</sub> ≤ 6.5%
- Weight
- FPG and 8-point SMPG



- Fasting insulin, proinsulin to insulin ratio, C-peptide, and HOMA
  - Fasting lipid profile
  - Systolic and diastolic blood pressure
  - Waist circumference and BMI
- Safety**
- Clinical evaluations (physical examination including ophthalmoscopy and vital signs.)
  - Electrocardiography (ECG) with rhythm strip
  - Laboratory tests (hematology, chemistry including calcitonin, amylase, and lipase, first morning urinalysis, and microalbumin creatinine ratio)
  - Formation of liraglutide antibodies
  - Assessment of compliance
  - Local site reactions
  - Growth velocity
  - Pubertal progression (Tanner Staging), LH, FSH, estradiol in females and testosterone in males
  - Hypoglycaemic episodes
  - Adverse Events / Serious Adverse Events

**Timing of assessments:**

SEE ABOVE

b/c

patients per group or 160 patients total.

**Timeframe for submitting reports of the studies:**

Final study report for PK/PD study: Date not included in current submissions. Sponsor has been requested to provide this information.

Final study report for efficacy and safety trial: \_\_\_\_\_

**Comments on Drug safety:**

The following safety information is excerpted from the Executive Summary of the clinical safety review. It represents the opinion of the clinical safety reviewer, and has not been signed off on by the clinical team leader.

For the clinical safety reviewer, there were two major safety concerns that affected approvability; inadequate data to assess the human risk of medullary thyroid carcinoma, and inadequate data to assess the risk of major adverse cardiovascular events.

In lifetime carcinogenicity studies in rats and mice, liraglutide caused C-cell tumors in both species, in both genders, at clinically relevant exposures. In rats, adenomas and carcinomas occurred in both genders at clinically relevant exposures. In mice, adenomas occurred at clinically relevant exposures, but carcinomas were seen only in females at high exposures. However, in rodents, C-cell adenomas are considered to be a precancerous lesion. There was a long latent period between initial exposure and development of C-cell tumors. A similar signal is being noted in interim carcinogenicity data for other long-acting glucagon-like-peptide-1 analogues. In rodents, calcitonin may not have been a reliable biomarker for development of these tumors; in humans, serum calcitonin has historically served as a clinical marker for medullary thyroid carcinoma, the human form of C-cell carcinoma. Calcitonin physiology differs somewhat between rodents and humans, and rodent thyroids may be more likely to contain glucagon-like-peptide-1 receptors. The applicability of these rodent findings to the risk of human medullary thyroid carcinoma is uncertain. In a meeting of the Endocrine and Metabolic Drugs Advisory Committee, the Committee voted 12 to 1 that the applicant had not established that the

b(4)

rodent C-cell tumor risk was not relevant to humans.

Medullary thyroid carcinoma is ordinarily a rare tumor, which occurs in sporadic and familial forms. No drug-induced forms have been described in humans. The described sporadic and familial forms are usually, although not always, indolent in terms of rate of growth. Although usually indolent in terms of rate of growth, the tumor can be aggressively invasive if not discovered in time for complete resection, and medullary thyroid carcinoma is considered to be a more serious form of thyroid cancer than the more common differentiated thyroid cancers. Early complete surgical resection is currently the only curative option. Those who undergo complete resection usually survive, and go on to die of something other than medullary thyroid cancer. However, the outcome for nonresectable cases is much worse, with a median survival of 3.2 years, and with medullary thyroid cancer as the usual cause of death. In these patients, local neck invasion, with asphyxia or other catastrophic local invasive process, is often the cause of death.

In the liraglutide program, there were no treatment-emergent cases of medullary thyroid carcinoma, but one might not expect to see this relatively indolent tumor over the duration of the typical drug development program.

A total of five liraglutide-treated patients and one comparator-treated patient had C-cell hyperplasia. This corresponds to a ratio of about 2.5:1, since there were approximately twice as many liraglutide-treated patients as comparator-treated patients in the development program. There is controversy in the medical literature regarding whether C-cell hyperplasia is a preneoplastic lesion in humans, and C-cell hyperplasia has been noted at autopsy in some people who had no known thyroid disease prior to death.

Calcitonin is a peptide hormone which is synthesized primarily by the C-cells of the thyroid. There are multiple stimuli for release, including calcium, several gut hormones, proton pump inhibitors, and several disease states such as renal impairment. Historically, it was used as a screening test for medullary thyroid cancer in relatives of patients with known medullary thyroid cancer; this use has largely been replaced by assays for specific genetic mutations known to occur in the familial forms. Most patients with medullary thyroid cancer have marked elevations of calcitonin, to over 50 ng/L, while the upper limit of normal is 5 ng/L for women and 8.4 ng/L for men. Serum calcitonin was measured in the major Phase 3 trials of liraglutide.

In general, liraglutide did not cause marked changes in calcitonin levels. In the blinded controlled portions of trials (6 months in 4 trials and 1 year in 1 trial), mean calcitonin values remained near the lower limit of quantitation. In voluntary unblinded extension studies out to two years, mean calcitonin levels remained near the lower limit of quantitation, but dropout rates were high and somewhat different between treatment groups. Patients who began study with calcitonin elevations did not tend to develop progressive further increases in calcitonin over time. Among patients who began study with calcitonin values <50 ng/L, two liraglutide-treated

patients and one comparator-treated patient developed calcitonin levels >50 ng/L (ratio 1:1).

However, liraglutide may have had some effect on calcitonin levels. From baseline to 26 weeks (the end of the blinded controlled portion of the trials), there was a dose-dependent trend for women to shift from below the lower limit of quantitation to within the range of quantitation. Also, from baseline to 26 weeks, the percentage of patients who had any upward category shift in calcitonin levels was highest, in both genders, for patients treated with the highest proposed liraglutide dose, 1.8 mg. At Week 12, for comparisons of all doses of liraglutide to active control, and to placebo, mean percent changes in calcitonin values were statistically significantly higher for liraglutide. At 26 weeks, this remained true for comparisons of liraglutide to placebo, and a dose dependent trend was noted for comparisons to both active control and placebo. However, mean values in these analyses were near the lower limit of quantitation. The incidence of new elevations of calcitonin to >20 ng/L was numerically higher for liraglutide (0.88%) than for comparator (0.57%), and there appeared to be a dose-related trend. The highest percentage of patients who developed a new elevation of calcitonin to >20 ng/L was among patients in the liraglutide 1.8 mg group (1.39%). The clinical significance of small changes in calcitonin in this setting is uncertain.

When asked whether the available data on thyroid C-cell tumors permit marketing of liraglutide, the Advisory Committee vote was 6 “no”, 6 “yes”, and 1 “abstain”.

Most trials of liraglutide were 6 months or less in duration. Calcitonin data from voluntary unblinded extensions of two trials are available for up to two years for approximately 500 liraglutide-treated patients. In the clinical reviewer’s opinion, this duration of observation is not adequate to assess the human risk of this tumor, which may be relatively indolent in terms of expected rate of growth, but which can have very poor outcomes in unresectable cases. The applicant’s proposed labeling does not provide for monitoring with calcitonin, thyroid ultrasound, or thyroid physical examination.

Besides calcitonin, there are other potential biomarkers for medullary thyroid carcinoma, including procalcitonin and carcinoembryonic antigen.

Drugs for the treatment of type 2 diabetes have the potential to be prescribed for millions of patients, and inadequately assessed safety problems can have significant public health consequences. To address the deficiency related to inadequate assessment of human medullary thyroid cancer risk for liraglutide, the clinical safety reviewer recommends a longer duration randomized, controlled, blinded trial, that would include monitoring not only of calcitonin, but of these other biomarkers, with measurements at baseline and every three to six months. The applicant has already proposed a large cardiovascular outcomes trial which would include

approximately 9000 patients. The clinical reviewer recommends that, in that trial, the applicant measure these biomarkers as outlined, and perform an interim analysis of calcitonin, procalcitonin and carcinoembryonic antigen levels at three years of study in this trial (i.e. when the last enrolled patient has three years of follow-up). At three years of study, one would not expect to see actual cases of medullary thyroid carcinoma, but the proposed analyses of multiple biomarkers could provide a reasonable assessment of whether any degree of C-cell activation is going on. Three years is recommended because currently, there are limited data for calcitonin (but not for other biomarkers) from voluntary unblinded extensions out to two years. These extensions had high dropout rates that differed between treatment groups. At the Advisory Committee meeting, Dr. Burman, one of the thyroid cancer experts, recommended a longer period of observation, and measurement of additional biomarkers. If there is no evidence of C-cell activation, even over three years of study, this could provide some level of comfort that the likelihood of induction of an aggressive form of medullary thyroid cancer by liraglutide would be small. With this information in hand, the public health consequences related to medullary thyroid cancer risk for liraglutide could reasonably be expected to be relatively low.

The second safety concern which, in the clinical safety reviewer's opinion, affects approvability of liraglutide, is that of inadequate data to assess the risk of major adverse cardiovascular events. In a recent Guidance, the Agency outlined requirements for sponsors of new diabetes drugs to rule out unacceptably increased risk of cardiovascular events. There are multiple elements to the Guidance, but two relevant elements are inclusion in the development program of patients at high risk for cardiovascular events (which permits accrual of sufficient events for analysis), and premarket exclusion of a certain level of increased cardiovascular risk. Events of interest include a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. The liraglutide NDA had already been submitted at the time of finalization of the Guidance, but the Agency has stated that it and other applications in the same circumstance must also meet the requirements of the Guidance.

The liraglutide trials excluded patients with known cardiovascular disease, and event rates were very low. In a composite of event terms deemed likely to represent true events of cardiovascular death, myocardial infarction or stroke, there were only 26 total events (liraglutide and comparator combined) during the controlled, blinded portions of the trials, and only 23 of these events met the definition of a serious adverse event. In general, stratified analyses of liraglutide versus total comparator (active control plus placebo) did have point estimates which favored liraglutide, and upper bounds of the 95% confidence interval of <1.8, which was the prespecified upper boundary that could permit approval of a diabetes drug with a requirement for a large postmarketing cardiovascular outcomes trial. The Guidance does not require applicants to meet specified confidence interval boundaries for subgroup analyses. However, subgroups were analyzed for consistency of the findings. Analyses of liraglutide versus active comparator were qualitatively similar to those versus total comparator. Analyses of liraglutide versus placebo, however, were sensitive to analysis method, and sometimes had point estimates >1, not favoring liraglutide, and upper bounds of 95% confidence intervals which

exceeded 1.8. The finding of upper bounds that sometimes exceeded 1.8 can be attributed in large part, to very low event rates. The finding of point estimates that sometimes exceeded 1 cannot be attributed to lower cardiovascular risk among placebo-treated patients, as these analyses were stratified by study, and baseline risk was similar between treatment arms in each of the included studies. Analyses by baseline duration of diabetes (<10 years or  $\geq 10$  years) also showed point estimates  $> 1$ , and upper bounds  $> 1.8$ , for comparisons of liraglutide versus placebo, particularly when one considered patients who had had diabetes for  $< 10$  years at baseline. This was not an expected finding, as the risk of cardiovascular events is generally thought to be higher in patients with diabetes of longer duration, but very low event rates limited interpretability.

In the Advisory Committee meeting, data regarding major adverse cardiovascular events were presented to the panel, which included two cardiologists and a biostatistician, in addition to endocrinologists, an epidemiologist, a patient representative and a consumer representative. The panel's overall vote was 8 "yes" and 5 "no" regarding whether the applicant had ruled out an unacceptable increase in cardiovascular risk. However, both cardiologists and the biostatistician voted "no", citing concerns about small numbers of events, low cardiovascular risk of the studied population, and the difference in results for analyses versus placebo. Other panel members, including some who voted "yes", also expressed concerns about the adequacy of the data.

There are several other safety concerns for liraglutide, but, in the clinical reviewer's opinion, these other issues, while potentially important, can be addressed through labeling and/or future studies, and do not rise to the level of approvability issues. They include:

- A numerical imbalance in cases of papillary thyroid cancer, not favoring liraglutide (6 cases versus 1; ratio 3:1). Almost all of these cancers were  $< 1$  cm, and were discovered at surgery that was prompted by routine protocol-specified calcitonin or ultrasound screening. They are likely incidental papillary microcarcinoma, which are common in the general population. However, ascertainment issues cannot fully explain the imbalance, because screening occurred for both liraglutide and comparator groups, and one would expect a similar rate of incidental papillary cancers if this observation was entirely related to increased screening.
- Gastrointestinal adverse events, especially nausea, vomiting and diarrhea. Rates of withdrawals due to gastrointestinal adverse events were higher for liraglutide-treated patients, and gastrointestinal events occurred with higher frequency when liraglutide was combined with metformin than when metformin was administered alone.
- Pancreatitis. There were 8 events of pancreatitis among liraglutide-treated patients, and 1 among comparator-treated patients (ratio 4:1). One liraglutide-treated case was fatal, although there were confounding elements to this case. The comparator group patient, and four of the liraglutide group patients, had risk factors for pancreatitis. Pancreatitis may be a class effect for glucagon-like-peptide-1 analogues, given recent postmarketing reports for exenatide, for which final labeling discussions are ongoing.
- Serious neoplasm events. In the original New Drug Application, serious neoplasm events occurred at rates of 8.9 versus 5.3 events

per 1000 patient-years for liraglutide versus total comparator. After the 120-day safety update, these rates were 12.3 versus 8.1. After removal of serious but nonmalignant neoplasms, and papillary thyroid cancers, these rates were 10.3 versus 8.1 events per 1000 patient years. No particular cancer cell type predominated. There have been recent concerns, based on epidemiologic data (some of which are conflicting), of a possible association between insulin and increased risk of malignancy. Liraglutide causes an increase in insulin levels. This risk should be further assessed in future trials of liraglutide.

- Serious hypoglycemic events. In the major Phase 3 trials submitted with the NDA, all serious hypoglycemic events (defined as events requiring the assistance of another person) occurred among liraglutide-treated patients, with none among comparator-treated patients. Six of these 9 events occurred among patients concomitantly administered a sulfonylurea. The risk for this may be similar between liraglutide and exenatide; in recent preliminary results of a comparative trial, two exenatide-treated patients and one liraglutide-treated patient had serious hypoglycemic events.
- Injection site reactions were more common among liraglutide-treated patients than among comparator-treated patients, and liraglutide dose-dependency was noted.
- Antibodies to liraglutide developed in approximately 10% of liraglutide-treated patients, and antibodies which cross-reacted with native glucagon-like-peptide-1 developed in about 5% of patients. About 1-2% of liraglutide-treated patients developed antibodies which had a neutralizing effect on liraglutide in an *in vitro* assay. However, efficacy as measured by hemoglobin A1c was not affected by antibody formation. Antibody-positive patients were more likely to have events related to infections; most of these were nonserious nasopharyngeal or upper respiratory infections. Antibody-positive patients also had more events of musculoskeletal pain and of certain injection site adverse reactions.
- Immunogenicity events from standardized queries using the Medical Dictionary for Regulatory Activities were more common among liraglutide-treated patients than among comparator-treated patients. About 40% of immunogenicity-related events were urticaria events.
- Slowing of gastric emptying, with effects on the pharmacokinetics of other drugs. The clinical significance of this effect is under discussion with the Clinical Pharmacology team.
- Overall thyroid neoplasms (19 versus 4 for liraglutide versus comparator; ratio 2.4:1). These were mostly thyroid nodules discovered after protocol-specified screening.
- Hepatobiliary adverse events. Overall rates of hepatobiliary adverse events were similar for liraglutide and comparator, but all withdrawals due to hepatobiliary adverse events (n=5) occurred among liraglutide-treated patients. A higher numerical percentage of liraglutide-treated patients had bilirubin levels above the upper limit of normal. There was no difference between liraglutide and comparator for transaminase elevations. No patients met the criteria for Hy's law.
- A small increase in heart rate of 2-3 beats per minute, and a numerical imbalance in adverse events related to increased heart rate,

not favoring liraglutide. A "thorough QT study" did not show evidence of a liraglutide-associated risk of QT prolongation.

- Risk of medication errors due to design and labeling of the pen injector — The applicant is submitting a new pen device to address these concerns, and reviews by the Chemistry, Manufacturing and Controls reviewer and the Devices reviewer are ongoing.

- Potential for off-label use/abuse for weight loss. Liraglutide was associated with a small amount of weight loss in clinical trials.

- Potential exists for off-label use in a non-diabetic population that would not benefit from liraglutide's glucose-lowering effects, but could still be at risk for all its adverse effects.

- Animal fetal anomalies at exposures at or below that expected for the human clinical dose. Pregnancy Category C is recommended by the Pharmacology/Toxicology review team.

- Nonserious adverse events of dizziness and fatigue.



## Debarment Certification

Novo Nordisk Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US,  
o=Novo Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.05.13 15:16:57 -0400

---

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Mary Ann McElligott, Ph.D.		TITLE Associate Vice President, Regulatory Affairs	
FIRM / ORGANIZATION Novo Nordisk Inc.			
SIGNATURE Mary Ann McElligott		<small>Digitally signed by Mary Ann McElligott DN: cn=Mary Ann McElligott, o=US, o=Novo Nordisk, ou=Regulatory Affairs, email=MAMC@NovoNordisk.com Date: 2008.05.19 13:00:52 -0400</small>	DATE 5/23/08

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857



49 Page(s) Withheld

√ Personal Privacy Information (b6)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

## DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning see attached lists of US investigators, who participated  
Name of clinical investigator  
as a clinical investigator in the submitted study see attached list of US studies  
Name of  
clinical study, is submitted in accordance with 21 CFR part 54. The  
named individual has participated in financial arrangements or holds financial interests that are  
required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Mary Ann McElligott, Ph.D.	TITLE Associate Vice President, Regulatory Affairs
FIRM / ORGANIZATION Novo Nordisk Inc.	
SIGNATURE Mary Ann McElligott <small>Digitally signed by Mary Ann McElligott DN: cn=Mary Ann McElligott, c=US, ou=Novo Nordisk, ou=Regulatory Affairs, email=MAMC@NovoNordisk.com Date: 2008.05.19 13:01:12 -0400</small>	DATE 5/23/08

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

## Tables of Financial Disclosure for US Trials

### Investigator Disclosure Information

**Trial Name**

Minimization of Bias

**b(6)**

**Table for Financial Disclosure Review**

Study # \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_  
Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_  
Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each	Disclosable Information** (Yes/No)
-------------	--------------------------------------	--------------------------------------	--	--	------------------------------------

b(6)

\*If No information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

b(

Financial Disclosure Form  
ClinSite CRA Training Manual  
Revised 03/01/2005

**NOVO NORDISK INC.**  
**Certification: Financial Interests and Arrangements of Clinical**  
**Investigators**  
**(per 21 CFR Part 54)**

**Protocol Title: Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type 2 Diabetes [A Fifty-Two Week (with Fifty-Two Week Open-label Extension), Double-Blind, Multicenter, Randomized, Parallel Study to Investigate Safety and Efficacy]**

Trial ID: \_\_\_\_\_

**Please check A or B:**

A.  As a Principal Investigator or sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.

1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.

B.  The details of my disclosable financial arrangements are attached.

Signature: \_\_\_\_\_

Date: 4/05/08

Name and Address:

Telephone:

Name of Institution (if applicable):

b(6)

b(6)



Attachment to Financial Disclosure - Section "B"  
Details of disclosable financial arrangements

Trial ID:	_____
Site Name:	_____
Financial Disclosure for Clinical Investigator (name):	_____

b(6)

For this purpose, you need to disclose financial arrangements with **Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates** including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.

**Definition of Clinical Investigator** - Principal investigator or Sub-investigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.

1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?

Yes  No

If Yes, please explain (size and nature of financial interest):

1b. Any equity interest in NNI that exceeds \$50,000 in value?

Yes  No

If Yes, please explain (size and nature of financial interest):

2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?

Yes  No

If Yes, please explain (size and nature of financial interest):

3. Significant payments of other sorts which have a **cumulative** monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?

Yes  No

If Yes, please explain (size and nature of financial interest):

\_\_\_\_\_ \$25K, \_\_\_\_\_ \$50K

b(6)

I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. if there is any change in this information from now until up to one (1) year after the completion of the trial.

\_\_\_\_\_

4/09/08  
Date

b(6)

Financial Disclosure Form  
ClinSite CRA Training Manual  
Revised 03/01/2005

**NOVO NORDISK INC.**  
**Certification: Financial Interests and Arrangements of Clinical  
Investigators**  
**(per 21 CFR Part 54)**

Protocol Title: **Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type 2 Diabetes [A Fifty-Two Week (with Fifty-Two Week Open-label Extension), Double-Blind, Multicenter, Randomized, Parallel Study to Investigate Safety and Efficacy]**

Trial ID: \_\_\_\_\_

**Please check A or B:**

A.

As a Principal Investigator or sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.

1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.

B.

The details of my disclosable financial arrangements are attached.

Signature: \_\_\_\_\_

Date: 4/30/08

Name and Address: \_\_\_\_\_

Telephone: \_\_\_\_\_

Name of Institution (if applicable): \_\_\_\_\_

b(6)

b(6)

**Attachment to Financial Disclosure - Section "B"**  
**Details of disclosable financial arrangements**

<b>Trial ID:</b>	/
<b>Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> - Principal investigator or Sub-investigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b> <span style="float: right; margin-right: 50px;">7000 shares</span></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. if there is any change in this information from now until up to one (1) year after the completion of the trial.</p>	
<b>Signature</b>	/
<b>Print Name</b>	/
	Date <u>4/30/08</u>

b(6)

b(6)

**Table for Financial Disclosure Review**

Study # \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: 14/Aug/2007

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each Investigator* (yes/no)	Disclosable Information** (yes/no)

b(6)

\*If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

Financial Disclosure Form  
ClinSite CRA Training Manual  
Revised 03/01/2005

**NOVO NORDISK INC.**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**  
**(per 21 CFR Part 54)**

Protocol Title: Liraglutide Effect and Action in Diabetes (Lead-4): Effect on Glycemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)	
Trial ID: _____	
<b>Please check A or B:</b>	
A. <input type="checkbox"/>	As a Principal Investigator or sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable. <ol style="list-style-type: none"> <li>Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.</li> <li>Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</li> <li>Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the Institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.</li> <li>I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</li> </ol>
B. <input checked="" type="checkbox"/>	The details of my disclosable financial arrangements are attached.
	Date: <u>4/7/08</u>
Name and Address:	_____
Telephone:	_____
Name of Institution (if applicable):	_____

b(6)

b(6)



Financial Disclosure Form  
ClinSite CRA Training Manual  
Revised 03/01/2005

**NOVO NORDISK INC.**  
**Certification: Financial Interests and Arrangements of Clinical**  
**Investigators**  
**(per 21 CFR Part 54)**

Protocol Title: Liraglutide Effect and Action in Diabetes (Lead-4): Effect on Glycemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)

Trial ID: \_\_\_\_\_

b(6)

**Please check A or B:**

- A.  As a Principal Investigator or sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.
1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.
  2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.
  3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.
  4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.

B.  The details of my disclosable financial arrangements are attached.

Signature: \_\_\_\_\_

Date: 4/30/08

Name and Address: \_\_\_\_\_

Telephone: \_\_\_\_\_

Name of Institution (if applicable): \_\_\_\_\_

b(6)

### Attachment to Financial Disclosure - Section "B" Details of disclosable financial arrangements

<b>Trial ID:</b>	/
<b>Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	

b(6)

For this purpose, you need to disclose financial arrangements with **Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates** including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.

**Definition of Clinical Investigator** - Principal investigator or Sub-investigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.

1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?  
 Yes  No   
**If Yes, please explain (size and nature of financial interest):**

1b. Any equity interest in NNI that exceeds \$50,000 in value?  
 Yes  No   
**If Yes, please explain (size and nature of financial interest):** 2000 mm

2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?  
 Yes  No   
**If Yes, please explain (size and nature of financial interest):**

3. Significant payments of other sorts which have a **cumulative** monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?  
 Yes  No   
**If Yes, please explain (size and nature of financial interest):**

I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. if there is any change in this information from now until up to one (1) year after the completion of the trial.

Signature \_\_\_\_\_ Date 4/30/01

Print Name \_\_\_\_\_

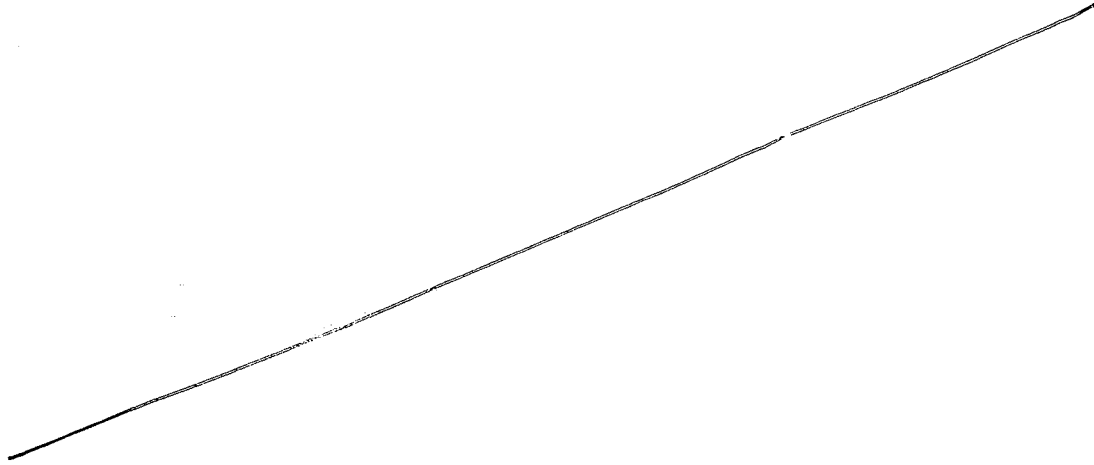
b(6)



**Table for Financial Disclosure Review**

Study # \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each Investigator* (Yes/No)	Disclosable Information** (Yes/No)
USA					



**b(6)**

\*If No information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

NOVO NORDISK PHARMACEUTICALS, INC. (NNPI)  
Certification: Financial Interests and Arrangements of Clinical Investigators  
(per 21 CFR Part 54)

Protocol Title: NNC 90-1170 dose-response, efficacy, and safety: a 12-week randomized, multi-center, double-blind, double-dummy, parallel-group study of metformin and five doses of NNC 90-1170 in previously treated OHA monotherapy obese subjects with type 2 diabetes

Trial ID: \_\_\_\_\_

Please check A or B:

A.  As a Principal Investigator or subinvestigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Pharmaceuticals, Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.

1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.

B.  The details of my disclosable financial arrangements are attached.

Signature: \_\_\_\_\_ Date: 11/28/07

Name and Address: \_\_\_\_\_

Telephone: \_\_\_\_\_

Name of Institution (if applicable): \_\_\_\_\_

b(6)

b(6)

\_\_\_\_\_  
Trial Agreement  
PI: \_\_\_\_\_

\_\_\_\_\_  
Trial I.D. No. Specify: G or SS  
\_\_\_\_\_  
Center # # Letter cc: Initials

NOVO NORDISK PHARMACEUTICALS, INC. (NNPI)  
Certification: Financial Interests and Arrangements of Clinical Investigators  
(per 21 CFR Part 54)

Protocol Title: NNC 90-1170 dose-response, efficacy, and safety: a 12-week randomized, multi-center, double-blind, double-dummy, parallel-group study of metformin and five doses of NNC 90-1170 in previously treated OHA monotherapy obese subjects with type 2 diabetes	
Trial ID: _____	
Please check A or B:	
A. <input checked="" type="checkbox"/> As a Principal Investigator or subinvestigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Pharmaceuticals, Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.	
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 11/16/00
Name and Address: _____	
Telephone: _____	
Name of Institution (if applicable): _____	

b(6)

b(6)

NOVO NORDISK PHARMACEUTICALS, INC. (NNPI)  
Certification: Financial Interests and Arrangements of Clinical Investigators  
(per 21 CFR Part 54)

Protocol Title: NNC 90-1170 dose-response, efficacy, and safety: a 12-week randomized, multi-center, double-blind, double-dummy, parallel-group study of metformin and five doses of NNC 90-1170 in previously treated OHA monotherapy obese subjects with type 2 diabetes	
Trial ID: _____	
Please check A or B:	
A. <input checked="" type="checkbox"/> As a Principal Investigator or subinvestigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Pharmaceuticals, Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.	
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 11/11/2000
Name and Address: _____	
Telephone: _____	
Name of Institution (if applicable): _____	

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**NOVO NORDISK PHARMACEUTICALS, INC. (NNPI)**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**  
**(per 21 CFR Part 54)**

Protocol Title: NNC 90-1170 dose-response, efficacy and safety: a 12-week randomized multicenter, double-blind double-dummy, parallel-group study of metformin and five doses of NNC 90-1170 in previously treated OHA monotherapy obese subjects with type 2 diabetes	
Trial ID: _____	
<b>Please check A or B:</b>	
A. <input checked="" type="checkbox"/>	As a Principal Investigator or subinvestigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Pharmaceuticals, Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.  1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.  2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.  3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.  4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.
B. <input type="checkbox"/>	The details of my disclosable financial arrangements are attached.
Signature: _____	Date: 4/25/02
Name and Address: _____	
Telephone: _____	
Name of Institution (if applicable): _____	

b(6)

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NOVO NORDISK PHARMACEUTICALS, INC. (NNPI)  
Certification: Financial Interests and Arrangements of Clinical Investigators  
(per 21 CFR Part 54)

Protocol Title: NNC 90-1170 dose-response, efficacy, and safety: a 12-week randomized, multi-center, double-blind, double-dummy, parallel-group study of metformin and five doses of NNC 90-1170 in previously treated OHA monotherapy obese subjects with type 2 diabetes	
Trial ID: _____	
<i>Please check A or B:</i>	
A. <input checked="" type="checkbox"/> As a Principal Investigator or subinvestigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk Pharmaceuticals, Inc., are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither I nor my immediate family own or control shares or American Depository Receipts of Novo Nordisk A/S whose value exceeds \$50,000.	
2. Neither I nor my immediate family have a proprietary interest (that is, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been hired by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000, exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there are any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 5-31-02
Principal Investigator <input type="checkbox"/>	OR Subinvestigator <input checked="" type="checkbox"/>
Name and Address: _____	
Telephone: _____	
Name of Institution (if applicable): _____	

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As per 21 CFR Part 54.4(a)(2)(v), the steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments are:

“The clinical trials were designed to reduce bias, as they were blinded, adequate well-controlled trials. Additionally many of the trials were conducted at multiple sites and were multi-national.”

## Tables of Financial Disclosure for non-US Trials

### Trial Name

\_\_\_\_\_

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**CERTIFICATION: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

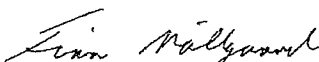
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached list of non-US investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Finn Møllgaard	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION Novo Nordisk A/S	
SIGNATURE 	DATE 5/23/08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

150 Page(s) Withheld

√ Personal Privacy Information (b6)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

**DISCLOSURE: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

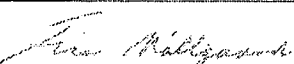
The following information concerning see attached list of non-US investigators, who participated  
Name of clinical investigator  
as a clinical investigator in the submitted study see attached list

Name of clinical study, is submitted in accordance with 21 CFR part 54. The  
clinical study  
named individual has participated in financial arrangements or holds financial interests that are  
required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Finn Møllgaard	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION Novo Nordisk A/S	
SIGNATURE 	DATE 5/23/08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

## Tables of Financial Disclosure for non-US Trials

### Investigator Disclosure Information

#### Trial Name

~~Minimization of Bias~~

**b(6)**

Minimization of Bias

**Table for Financial Disclosure Review**

Study #: \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each Investigator* (yes/no)	Disclosable Information** (yes/no)
/					

**b(6)**

\*If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

Novo Nordisk A/S

Novo Nordisk Certification:  
Financial Interests and Arrangements of Investigators  
(per 21 CFR Part 54)

Protocol Title: Dose-response relationship of five dose levels of NNC90-1170 and placebo on glycaemic control in type 2 diabetic patients compared to OHA treatment. A 12-week multi-centre, double-blind, randomised, parallel group trial with an open labelled OHA arm.	
Trial ID: _____	
Please tick A or B:	
A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000(USA).	
2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000(USA), exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 6/9/01
Name and Address: _____	
Telephone: _____	
Name of Institution (if applicable): _____	

b(6)

b(6)

5th April 2002

FAX: 01293613535

Melanie Cain  
Project Manager  
Novo Nordisk Ltd  
Broadfield Park  
Brighton Road  
CRAWLEY West Sussex  
RH11 9RT

Dear Melanie

RE: GLP1 study

I was contacted yesterday to say that page 2 of my financial disclosure for this study appears to be missing. On page 1, I was advised to declare a potential financial interest. On page 2 (missing) I felt it right to declare that NovoNordisk have recently given a grant of £50,000 to the

I trust this is all the information you require.

Yours sincerely

b(6)

Novo Nordisk A/S

Novo Nordisk Certification:  
Financial Interests and Arrangements of Investigators  
(per 21 CFR Part 54)

Protocol Title: Dose-response relationship of five dose levels of NNC90-1170 and placebo on glycaemic control in type 2 diabetic patients compared to OHA treatment. A 12-week multi-centre, double-blind, randomised, parallel group trial with an open labelled OHA arm.	
Trial ID: _____	
Please tick A or B:	
A. <input checked="" type="checkbox"/> As an Investigator or Sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000(USA).	
2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000(USA), exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 17/8/2001
Name and Address: _____	
Telephone: _____	
Name of institution (if applicable): _____	

b(6)



~~\_\_\_\_\_~~  
We hold various grants for Novo Nordisk which exceed \$25,000 and Novo Nordisk are part of a

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~ Novo Nordisk's contribution  
to this has been £ 1,000,000 in 1999 and £2,000,000 in 2000.

**b(6)**

~~\_\_\_\_\_~~

Novo Nordisk A/S

Novo Nordisk Certification:  
Financial Interests and Arrangements of Investigators  
(per 21 CFR Part 54)

<b>Protocol Title:</b> Dose-response relationship of five dose levels of NNC90-1170 and placebo on glycaemic control in type 2 diabetic patients compared to OHA treatment. A 12-week multi-centre, double-blind, randomised, parallel group trial with an open labelled OHA arm.	
<b>Trial ID:</b> _____	
<i>Please tick A or B:</i>	
A. <input type="checkbox"/> As an Investigator or Sub-investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000(USA).	
2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000(USA), exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.	
<b>Signature:</b> _____	<b>Date:</b> 29/8/07.
<b>Name and Address:</b> _____ _____ _____	
<b>Telephone:</b> <b>Name of Institution (if applicable):</b> _____	

b(6)

GRANTS AND GIFTS  
TO \_\_\_\_\_  
FROM NOVO NORDISK

• _____	£25,000	2000-2003
• _____	£25,000	2000-2001
TOTAL	<u>£50,000</u>	

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**Table for Financial Disclosure Review**

Study # \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each Investigator* (yes/no)	Disclosable Information** (yes/no)
				yes	YES
				yes	YES
				yes	YES
				yes	YES

b(1)

\*If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

## Novo Nordisk Certification: Financial Disclosure (per 21 CFR Part 54)

<b>Protocol Title:</b> _____ Dose-response relationship of five doses of liraglutide (NNC 90-1170) and placebo on glycaemic control in subjects with type 2 diabetes on diet therapy with or without OAD monotherapy	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<b>Please tick A or B:</b> _____	
<p><b>A. [ ]</b> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.</p> <p>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA)</p> <p>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</p> <p>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</p> <p>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</p>	
<p><b>B. [✓]</b> The details of my disclosable financial arrangements are attached.</p>	
<b>Signature:</b> _____	<b>Date:</b> 日付: Jul. 12. 2007
<b>Name and Address:</b> _____	
<b>Telephone:</b> _____	_____
<b>Name of Institution (if applicable):</b> _____	_____

b(6)

**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

<b>Trial ID:</b>	_____
<b>Study Site Name:</b>	_____
<b>Financial Disclosure for Clinical Investigator (name):</b>	_____
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.  <b>Definition of Clinical Investigator</b> – principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>  <b>If Yes, please explain (size and nature of financial interest):</b>          Donations: \$25,000          Honoraria: \$7,222</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>if there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
<p>_____  <b>Signature</b></p>	<p align="right">_____  <b>Date</b></p>
<p>_____  <b>Print Name</b></p>	

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**Novo Nordisk Certification:  
Financial Disclosure (per 21 CFR Part 54)**

<b>Protocol Title:</b> _____ Dose-response relationship of five doses of liraglutide (NNC 90-1170) and placebo on glycaemic control in subjects with type 2 diabetes on diet therapy with or without OAD monotherapy	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<b>Please tick A or B:</b>	
A. <input type="checkbox"/>	As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.
	<ol style="list-style-type: none"> <li>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).</li> <li>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial Interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</li> <li>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</li> <li>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</li> </ol>
B. <input checked="" type="checkbox"/>	The details of my disclosable financial arrangements are attached.
<b>Signature:</b> _____	<b>Date:</b> 日付: Jul. 31, 2007
<b>Investigator</b> _____ <b>OR</b> <b>Sub-Investigator</b> 治療分担医師 <input type="checkbox"/>	
<b>Name and Address:</b> _____	
<b>Telephone:</b> _____	
<b>Name of Institution (if applicable):</b> _____	

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**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

<b>Trial ID:</b>	
<b>Study Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> - principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b>          Donations: \$116,667          Honoraria: \$22,778</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>if there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
<p>_____  <b>Signature</b></p>	<p align="right"><u>Jul. 31. 2007</u>  <b>Date</b></p>
<p>_____  <b>Print Name</b></p>	

b(6)



**Novo Nordisk Certification:  
Financial Disclosure (per 21 CFR Part 54)**

<b>Protocol Title:</b> _____ Dose-response relationship of five doses of liraglutide (NNC 90-1170) and placebo on glycaemic control in subjects with type 2 diabetes on diet therapy with or without OAD monotherapy	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<b>Please tick A or B:</b> _____	
<p>A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.</p> <hr/> <p>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).</p> <hr/> <p>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</p> <hr/> <p>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</p> <hr/> <p>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</p> <hr/>	
<p>B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached. 添付書類に可能な資産運用の明細です</p>	
<b>Signature:</b> _____	<b>Date:</b> 日付: Jul. 17. 2007
<b>Name and Address:</b> _____	
<b>Telephone:</b> _____	
<b>Name of Institution (if applicable):</b> _____	

b(6)

**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

<b>Trial ID:</b>	
<b>Study Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> – principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b>          Donations: \$95,833          Honoraria: \$14,352</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>If there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
<p>_____  <b>Signature</b></p>	<p><u>Jul. 17. 2007</u>  <b>Date</b></p>
<p>_____  <b>Print Name</b></p>	

b(6)

# Novo Nordisk Certification:

## Financial Disclosure (per 21 CFR Part 54)

Protocol Title: _____ Dose-response relationship of five doses of liraglutide (NNC 90-1170) and placebo on glycaemic control in subjects with type 2 diabetes on diet therapy with or without OAD monotherapy	
Trial ID: _____	Investigator: _____
Please tick A or B: /	
A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).	
2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.	
3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.	
4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.	
Signature: _____	Date: 11/11/ Aug/9/2007
Name and Address:   _____	
Telephone: _____	
Name of Institution (if applicable): _____	

b(6)

**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

<b>Trial ID:</b> <b>Study Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> – principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b>          Honoraria: \$39,444</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>if there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
_____ <b>Signature</b>	_____ <b>Date</b>
_____ <b>Print Name</b>	Aug 19 / 2007

b(6)

**Novo Nordisk Certification:  
Financial Disclosure  
(per 21 CFR Part 54)**

<b>Protocol Title:</b> Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active controlled, parallel-group, multi-centre, multi-national trial.	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<i>Please tick A or B:</i>	
<p>A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.</p> <ol style="list-style-type: none"> <li>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).</li> <li>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</li> <li>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</li> <li>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</li> </ol>	
<p>B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.</p>	
<b>Signature:</b> _____	<b>Date:</b> 1/16/08
<b>Name and Address:</b> _____ _____ _____ _____ _____	
<b>Telephone:</b> _____ <b>Name of Institution (if applicable):</b> _____	

b(6)

**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

Trial ID:	
Study Site Name:	
Financial Disclosure for Clinical Investigator (name):	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> - principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>If Yes, please explain (size and nature of financial interest):</p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>If Yes, please explain (size and nature of financial interest):</p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>If Yes, please explain (size and nature of financial interest):</p>	
<p>3. Significant payments of other sorts which have a cumulative monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p>If Yes, please explain (size and nature of financial interest):</p> <p align="center" style="font-size: 1.2em;">\$ 55,000</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. if there is any change in this information from now until up to one (1) year after the completion of the study.</p>	
<p>Signature _____</p>	<p align="right">15/6/06 Date _____</p>
<p align="center">Print Name _____</p>	

b(6)

**Novo Nordisk Certification:  
Financial Disclosure  
(per 21 CFR Part 54)**

<b>Protocol Title:</b> Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of Liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial. Trial Phase: 3a	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<b>Please tick A or B:</b>	
<p>A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.</p> <ol style="list-style-type: none"> <li>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).</li> <li>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial Interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</li> <li>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</li> <li>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</li> </ol>	
<p>B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.</p>	
<b>Signature:</b> _____	<b>Date:</b> 13/2/06
<b>Name and Address:</b> _____	
<b>Telephone:</b> _____	
<b>Name of Institution (if applicable):</b> _____	

b(6)

**Attachment to Financial Disclosure - Section "B"**  
**details of disclosable financial arrangements**

<b>Trial ID:</b>	
<b>Study Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> - principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a <b>cumulative</b> monetary value of \$25,000 or more made by the Sponsor to the Investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p> <p>Since 1978 throughout my relationship with Novo Laboratories, CSL-Novo and Novo Nordisk, the I _____ will have received a cumulative amount greater than US\$25,000 from said companies. I have worked with these organisations as a _____ late 70s to the early 90s receiving an amount _____. From the late 90s I have worked as a _____, for Novo Nordisk each of which has had a different _____.</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>if there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
<p>_____          Signature</p>	<p>12/27/07          Date</p>
<p>_____          Print Name</p>	

b(6)



**Novo Nordisk Certification:  
Financial Disclosure  
(per 21 CFR Part 54)**

<b>Protocol Title:</b> Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active controlled, parallel-group, multi-centre, multi-national trial.	
Trial ID: _____	Investigator: _____
<b>Please tick A or B:</b>	
<p>A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.</p> <ol style="list-style-type: none"> <li>1. Neither my immediate family nor I own or control shares or (American/EU) Depository Receipts of Novo Nordisk whose value exceeds \$50,000 (USA).</li> <li>2. Neither I nor my immediate family have a proprietary interest (such as, a property or other financial interest, including but not limited to a patent, trademark, copyright or licensing agreement) in the product that I have been contracted by Novo Nordisk to test. "Financial interest" also includes an interest in a company that would benefit from approval of the product that I have been hired to test.</li> <li>3. Total payment (including research grants, donations of equipment, retainers, honoraria, etc.) by Novo Nordisk to me or the institution that is supporting the clinical trial activities will not exceed \$25,000 (USA), exclusive of the costs of conducting the clinical trial.</li> <li>4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.</li> </ol>	
<p>B. <input checked="" type="checkbox"/> The details of my disallowable financial arrangements are attached.</p>	
Signature: _____	Date: 15-6-04
Investigator <input checked="" type="checkbox"/> OR Sub-Investigator <input type="checkbox"/>	
<b>Name and Address:</b> _____ _____ _____ _____ _____	
<b>Telephone:</b> _____	
<b>Name of Institution (if applicable):</b> _____	

b(6)

**Attachment to Financial Disclosure - Section "B"  
details of disclosable financial arrangements**

<b>Trial ID:</b>	
<b>Study Site Name:</b>	
<b>Financial Disclosure for Clinical Investigator (name):</b>	
<p>For this purpose, you need to disclose financial arrangements with <b>Novo Nordisk A/S, Novo Nordisk Inc. or any other Novo Nordisk affiliates</b> including any or all companies owned or held by Novo Nordisk A/S or its subsidiaries.</p> <p><b>Definition of Clinical Investigator</b> – principal investigator or subinvestigator who is directly involved with treatment or evaluation of research subjects as well as the spouse and dependant children of the investigator.</p>	
<p>1a. Any ownership interest, stock options, or any other type of financial interest in NNI whose value can not be readily determined through reference to public prices?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>1b. Any equity interest in NNI that exceeds \$50,000 in value?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>2. Any proprietary interest such as patent, trademark, copyright, licensing, etc?          Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p><b>If Yes, please explain (size and nature of financial interest):</b></p>	
<p>3. Significant payments of other sorts which have a cumulative monetary value of \$25,000 or more made by the Sponsor to the investigator or the investigator's institution to support activities of the investigator, exclusive of the contracted costs of the study (such as consultation honoraria, grant to fund research, equipment, etc.)?          Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><b>Yes, please explain (size and nature of financial interest):</b></p> <p>GRANT OF AUS\$ 35,000 ANNUALLY FOR _____</p>	
<p>I certify that the information provided above is correct and complete. I understand that I am obligated to amend my documents disclosing my financial interests and arrangements and notify Novo Nordisk, Inc. <b>if there is any change in this information from now until up to one (1) year after the completion of the study.</b></p>	
<p>_____ Signature</p>	<p>15/6/06 _____ Date</p>
<p>_____ Print Name</p>	

b(6)

**Table for Financial Disclosure Review**

Study # \_\_\_\_\_ Study Start Date: \_\_\_\_\_ Study End Date: \_\_\_\_\_

Site Number	Number of Patients Entered Screening	Number of Patients Entered Treatment	Names of Investigators (principal and sub-investigators)	Certification and/or Disclosure for each Investigator* (yes/no)	Disclosable Information** (yes/no)
_____					

b(6)

\*If no information is provided by the investigator (principal or sub-investigator), then the sponsor must describe their efforts at due diligence in attempting to obtain this information, (i.e., sending certified letters, performing Internet searches, telephone calls, faxes, etc.)

\*\* Any and all disclosable financial information must be explained.

\*\*\*Joined during the extension

Novo Nordisk

**Novo Nordisk Certification:  
Financial Disclosure (per 21 CFR Part 54)**

<b>Protocol Title:</b> Liraglutide Effect and Action in Diabetes (LEAD-2): Effect on glycaemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months trial extension period	
<b>Trial ID:</b> _____	<b>Investigator:</b> _____
<b>Please tick A or B:</b>	
A. <input type="checkbox"/> As an Investigator or Sub-Investigator of the clinical trial noted above, I certify that the following statements regarding financial arrangements with the Sponsor, Novo Nordisk, are true in regard to myself as well as my immediate family (spouse and dependent children), if applicable.	
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4. I will notify Novo Nordisk if there is any changes in the information disclosed herein that occur during the clinical trial and for one year following completion of the trial.	
B. <input checked="" type="checkbox"/> The details of my disclosable financial arrangements are attached.	
<b>Signature:</b> _____	<b>Date:</b> 24/5/06
<b>Name and Address:</b>  _____	
<b>Telephone:</b> _____	
<b>Name of Institution (if applicable):</b> _____	

b(6)

May 24<sup>th</sup>, 2006

b(6)

Re: Financial Disclosure in respect of \_\_\_\_\_ Trial

To whom it may concern:

This is to state that the \_\_\_\_\_ receives an unrestricted grant annually of approximately \$45,000 to: \_\_\_\_\_

Yours sincerely,

\_\_\_\_\_  
\_\_\_\_\_

As per 21 CFR Part 54.4(a)(2)(v), the steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments are:

“The clinical trials were designed to reduce bias, as they were blinded, adequate well-controlled trials. Additionally many of the trials were conducted at multiple sites and were multi-national.”

08 - MAY - 2008

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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** January 12, 2010  
**TIME:** 3:00 PM  
**LOCATION:** CDER WO 1315 conf rm Bldg22 - AR  
**APPLICATION:** NDA 22-341  
**DRUG NAME:** Victoza (liraglutide)  
**TYPE OF MEETING:** Wrap-up and Pre-approval Safety Conference

**MEETING CHAIR:** Curtis Rosebraugh

**MEETING RECORDER:** John Bishai

### FDA ATTENDEES:

Aljuburi, Lina	(DMEP)	Mena-Grillasca, Carlos	(OSE)
Bishai, John	(DMEP)	Parks, Mary H	(DMEP)
Campbell, Cheryl	(OSE)	Parola, Anthony	(DMEP)
Choe, Sally	(OCP)	Porter, Brian	(PAP)
Davis Bruno, Karen L	(DMEP)	Ripper, Leah W	(ODE 2)
Diaz, Jessica M	(OSE)	Rosebraugh, Curtis	(ODE 2)
Egan, Amy	(DMEP)	Sahlroot, Jon T	(Biometrics)
Fava, Walter	(OSE)	Skariah, Sam	(DDMAC)
Joffe, Hylton	(DMEP)	Syed, Sajjad H	(CDRH)
Khurana, Manoj	(OCP)	Tossa, Margarita	(OSE)
Leginus, Joseph	(ONDQA)	Tran, Suong T	(ONDQA)
Leibenhaut, Susan	(DSI)	Worthy, Kendra	(OSE)
Mahoney, Karen M	(DMEP)	Wysowski, Diane K	(OSE)

### BACKGROUND:

Victoza is a glucagon-like peptide (GLP)-1 agonist developed for the treatment of type 2 diabetes mellitus. This new molecular entity (NME) is dosed once daily as compared to twice daily (Byetta) and is associated with both weight loss and a generally low risk for hypoglycemia. Victoza causes thyroid C-cell tumors in rats and mice, in both genders, at clinically relevant exposures. This finding in addition to the recent guidance for cardiovascular risk led an advisory committee hearing. Two votes at the committee were taken to determine the relevance of the non-clinical findings. The results were as follows:

- “Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?” One panel member voted “Yes” and the remaining 12 panel members voted “No”
- “Assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of liraglutide?” Six panel members voted “Yes”, six panel members voted “No”, and one panel member abstained.

Similar to these mixed results, the review team also had mixed views. Ultimately, the decision was elevated to the director of ODE 2, Curtis Rosebraugh, whom elected for application approval.

**MEETING OBJECTIVES:**

1. Discuss the approval of Victoza.
2. Discuss the proposed REMS proposal
3. Reiterate the post-marketing requirements (PMRs)

**DISCUSSION POINTS:**

Dr. Rosebraugh started the meeting explaining the rationale underlying his decision to approve Victoza. The meeting then turned to a brief overview of the REMS, postmarketing required studies, and remaining open items needing to be addressed before an action could be taken.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS (REMS)**

1. Medication Guide
2. Communication Plan
3. Timetable for submission of assessments

**POST MARKETING REQUIREMENTS (PMRs)**

1. Deferred phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3b study that will be conducted under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

Final Protocol Submission:	<b>March 26, 2009</b>
Study Completion Date:	<b>June 30, 2010</b>
Final Report Submission:	<b>October 31, 2010</b>

2. Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.



Final Protocol Submission: **July 31, 2012**  
Study Completion Date: **November 30, 2015**  
Final Report Submission: **March 30, 2016**

3. A 2-year study in mice to determine if 26 weeks of liraglutide treatment increases the lifetime risk of thyroid C-cell tumors. The study must include a 26-week interim sacrifice group to determine the incidence of focal C-cell hyperplasia and tumors at the end of the treatment period.

Final Protocol Submission: **July 31, 2010**  
Study Completion Date: **January 31, 2013**  
Final Report Submission: **July 31, 2013**

4. A 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant type 2 diabetes mellitus. This study must include monitoring biomarkers for pancreatitis (amylase, lipase) and glucose-lowering efficacy (HbA1c) during the treatment period and a thorough assessment of macroscopic and microscopic pathology of the pancreas including pancreatic exocrine cell and ductal cell proliferation/metaplasia. Reversibility of any effects on the pancreas must also be determined.

Final Protocol Submission: **July 31, 2010**  
Study Completion Date: **May 30, 2011**  
Final Report Submission: **July 31, 2011**

5. A 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid glucagon-like peptide-1 (GLP-1) receptor and rearranged during transfection (RET) proto oncogene activation. Autoradiographic ligand binding in thyroid tissue sections can be used to determine GLP-1 receptor localization in mice with and without focal C-cell hyperplasia. RET activation and downstream signaling must be assessed in normal C-cells and focal hyperplastic C-cells from mouse thyroid tissue sections.

Final Protocol Submission: **July 31, 2010**  
Study Completion Date: **May 30, 2011**  
Final Report Submission: **July 31, 2011**

6. A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza and patients with type 2 diabetes not exposed to Victoza, as well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms.

Final Protocol Submission: **April 30, 2010**  
Study Completion Date: **July 31, 2015**

Final Report Submission:

**January 31, 2016**

7. Medullary thyroid carcinoma case series registry 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 Victoza 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 Victoza.

Final Protocol Submission:

**July 31, 2010**

Study Completion Date:

**September 15, 2025**

Final Report Submission:

**September 15, 2026**

8. Submission of the complete final study report for Study 1797, a head-to-head efficacy and safety comparison of Victoza and exenatide.

Final Report Submission:

**February 26, 2010**

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. This trial must also assess adverse events of interest including the long-term effects of Victoza on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

Final Protocol Submission:

**March 14, 2010**

Study Completion Date:

**September 14, 2015**

Final Report Submission:

**April 30, 2016**

**Open Items to be Resolved Prior to Approval**

1. Align pancreatitis language in PI, REMS, AP letter, and Medication Guide
2. Revise the language describing the safety margins for the thyroid C-cell carcinomas in the Warnings and Precautions section of the PI and in the Press Release so that the language is fully consistent with the corresponding language in the Non-Clinical section of the PI.
3. Tradename re-review (prior approval expires 1/21/10)
4. OSE REMS review and Medication Guide review
5. Finalize the Information Advisory and have it cleared for sending to HHS
6. Ensure the PMR dates in AP letter reflect the most recent agreed upon dates.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
JDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)
NDA-22341	PMR/PMC-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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

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/s/

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JOHN M BISHAI  
01/21/2010

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Deferred phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3b study that will be conducted under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years  
11 months

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PMR/PMC Schedule Milestones: Final protocol Submission Date: NA  
Study/Clinical trial Completion Date: 06/30/2010  
Final Report Submission Date: 10/31/2010  
Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Liraglutide is ready for approval for use in adults. However, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Deferred pediatric study required under PREA in pediatric patients ages 10 to 16 years with type 2 diabetes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A phase 1 pharmacokinetic dose finding study of liraglutide in pediatric patients ages 10 to 16 years 11 months.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Subpopulation: Pediatric patients ages 10-16 years 11 months with type 2 diabetes mellitus

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2012  
Study/Clinical trial Completion Date: 11/30/2015  
Final Report Submission Date: 03/30/2016  
Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Liraglutide is ready for approval for use in adults. However, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Deferred pediatric study required under PREA in pediatric patients ages 10 to 16 years 11 months with type 2 diabetes. The goal of the trial is to establish the safety and efficacy of liraglutide in this sub-population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of liraglutide in pediatric patients ages 10 to 16 years 11 months.

Required

- Observational pharmacoepidemiologic study
- Registry studies



Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Subpopulation: Pediatric patients ages 10-16 years 11 months with type 2 diabetes mellitus

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: A 2-year study in mice to determine if 26-weeks of liraglutide treatment increases the lifetime risk of thyroid C-cell tumors

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2010  
Study/Clinical trial Completion Date: 01/31/2013  
Final Report Submission Date: 07/31/2013  
Other: NA

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Victoza (liraglutide for injection), a long-acting GLP-1 receptor agonist, is a nongenotoxic carcinogen causing thyroid C-cell tumors in both genders of mice and rats exposed to the drug over a lifetime (2 years). Although the human risk of liraglutide-induced C-cell tumors is unknown, there was no evidence of drug-induced C-cell tumors in clinical studies of Victoza. It is not known if shorter term exposures in mice increase their lifetime risk of developing thyroid C-cell tumors.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new-safety information."

In carcinogenicity studies in rats and mice exposed to liraglutide for most of their lifetime, liraglutide caused thyroid C-cell tumors in both rats and mice after more than 26 weeks of treatment. In mice, preneoplastic focal C-cell hyperplasia occurred after only 4 weeks of treatment. The goal of this study is to determine if a liraglutide treatment duration long enough to induce preneoplastic focal C-cell hyperplasia, but not C-cell tumors, increases the lifetime risk of thyroid C-cell tumors in mice.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In this 104-week study, mice will be treated with liraglutide at doses and treatment durations that induce preneoplastic focal C-cell hyperplasia (26 weeks of treatment, ~25% of their total lifespan), but not C-cell tumors, and the incidence of C-cell tumors will be determined for up to 78 weeks after treatment is stopped. This study should include a 26-week interim sacrifice group to determine the incidence of focal C-cell hyperplasia and tumors at the end of the treatment period.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: A 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of type 2 diabetes

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2010  
Study/Clinical trial Completion Date: 05/30/2011  
Final Report Submission Date: 07/31/2011  
Other: NA

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Postmarketing reports of pancreatitis in patients treated with an approved GLP-1 receptor agonist (exenatide), a numerical imbalance in the incidence of pancreatitis in clinical studies of liraglutide not favoring the drug, and 2 published nonclinical studies of incretin-based drugs suggest GLP-1 receptor agonists and DPP-4 inhibitors may increase the risk of pancreatitis in patients with type 2 diabetes. The incidence of pancreatitis in clinical trials of liraglutide was low. In repeat dose toxicity studies in euglycemic mice, rats, and monkeys, liraglutide did not have any pronounced effect on the exocrine pancreas consistent with pancreatitis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Postmarketing reports of pancreatitis in patients treated with an approved GLP-1 receptor agonist (exenatide), a numerical imbalance in the incidence of pancreatitis in clinical studies of liraglutide not favoring the drug, and 2 published nonclinical studies of incretin-based drugs suggest liraglutide may increase the risk of pancreatitis in patients with type 2 diabetes. Diabetics are at an increased risk for pancreatitis and GLP-1 receptor agonists may increase that risk. Although repeat dose toxicity studies in euglycemic animals did not suggest a risk of liraglutide-induced pancreatitis, the effect of liraglutide on the exocrine pancreas in animal models of type 2 diabetes was not determined. The goal of this study is to determine if liraglutide causes pancreatitis or microscopic pathology changes associated with pancreatitis in a rodent model of type 2 diabetes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The objective of this study is to determine the effect of 3 months of treatment with liraglutide on the pancreas in a rodent model of insulin resistant type 2 diabetes. This study will include monitoring biomarkers for pancreatitis (amylase, lipase) and glucose-lowering efficacy (HbA1c) during the treatment period and a thorough assessment of macroscopic and microscopic pathology of the pancreas including pancreatic exocrine cell and ductal cell proliferation / metaplasia. Reversibility of any effects on the pancreas should also be determined.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: A 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP-1 receptor and RET activation

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2010  
Study/Clinical trial Completion Date: 05/30/2011  
Final Report Submission Date: 07/31/2011  
Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Victoza (liraglutide for injection), a long-acting GLP-1 receptor agonist, is a nongenotoxic carcinogen causing thyroid C-cell tumors in both genders of mice and rats exposed to the drug over a lifetime (2 years). Although the human risk of liraglutide-induced C-cell tumors is unknown, liraglutide did not cause C-cell tumors in clinical studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In carcinogenicity studies in rats and mice exposed to liraglutide for most of their lifetime, liraglutide caused thyroid C-cell tumors in both rats and mice after more than 26 weeks of treatment. A published autoradiographic ligand binding study showed approximately 60% of mice and 5% of humans were thyroid GLP-1 receptor positive. In humans, activating mutation in the REarranged during Transfection (RET) protooncogene is the primary cause of familial MTC and the most common cause of spontaneous MTC. It is not known if a thyroid GLP-1 receptor is required for drug-induced C-cell tumors or if liraglutide causes rodent C-cell tumors by a RET-dependent pathway. The goal of this study is to determine if liraglutide-induced focal C-cell hyperplasia occurs in thyroid GLP-1 receptor negative mice and if liraglutide activates RET signaling in normal and focal hyperplastic C-cells.



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Mice will be treated with liraglutide for 13 weeks using doses that induce focal C-cell hyperplasia. Autoradiographic ligand binding in thyroid tissue sections can be used to determine GLP-1 receptor localization in mice with and without focal C-cell hyperplasia. RET activation and downstream signaling will be assessed in normal C-cells and focal hyperplastic C-cells from mouse thyroid tissue sections.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See #1 above for description of review issue and risk. The goal of the epidemiologic study is to obtain information on the incidence of thyroid cancer, macrovascular adverse events, pancreatitis, serious hypoglycemic events and overall malignant neoplasms in initiators of liraglutide, compared to initiators of other antidiabetic agents, over time.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A five year epidemiologic study of 150,000 patients, 25,000 of whom are treated with liraglutide, to be conducted using a large health care claims database. In the study, all initiators of liraglutide in the database will be matched by baseline characteristics (using propensity score matching) to initiators of other antidiabetic agents. The primary endpoint will be the occurrence of thyroid cancer (cell type not specified). Although medullary thyroid cancer is the cancer cell type of greatest interest, there is no specific diagnosis code for this cancer under the International Classification of Diseases coding system. For all thyroid cancer cases identified in this epidemiologic study, medical records review should occur to determine the actual thyroid cancer cell type.

Other endpoints will include, but are not limited to, hypoglycemia resulting in an emergency department visit or hospitalization; pancreatitis; macrovascular events (myocardial infarction and stroke); and overall malignant neoplasms.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)
- 
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: Medullary Thyroid Carcinoma Case Series Registry

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>07/31/2010</u>
	Study/Clinical trial Completion Date:	<u>09/15/2025</u>
	Final Report Submission Date:	<u>09/15/2026</u>
	Other: Annual reports due on the last Friday of August of each year from 2012-2025.	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Liraglutide causes C-cell tumors in two animal species, in both genders, at clinically relevant exposures, in a dose-dependent and time-dependent manner. Cases of medullary thyroid carcinoma (human C-cell cancer) were not seen in clinical trials, but the duration of blinded controlled study was not adequate to assess the risk fully in the premarketing setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See #1 for the review issue. The goal of the registry is to detect the majority of cases of medullary thyroid carcinoma which occur in North America over the twenty year period after marketing approval of VICTOZA® (liraglutide), to evaluate all cases for risk factors for medullary thyroid carcinoma and for exposure to diabetes medications, and to determine whether there is a relationship between liraglutide exposure and risk for medullary thyroid carcinoma.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A case series registry which seeks to identify all possible cases of medullary thyroid carcinoma which occur in North America during the twenty year period after approval of VICTOZA® (liraglutide). Ascertainment of cases should be as extensive as possible, including such sources as cancer registries; cancer center hospitals; medical centers with endocrinology fellowship programs; and professional organizations such as the American Thyroid Association, North American members of the International Thyroid Oncology Group, The Endocrine Society and the American Association of Clinical Endocrinologists. All cases will be evaluated for risk factors for medullary thyroid carcinoma and for exposure to liraglutide or other diabetes medications. Analyses will be conducted to determine whether liraglutide appears to be a risk factor for medullary thyroid carcinoma. Reporting is to occur annually.



Required

- Observational pharmacoepidemiologic study
- Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Submission of complete final study report for trial 1797 (head-to-head efficacy and safety comparison of liraglutide vs. exenatide, the only FDA-approved GLP-1 agonist). This trial was completed after the liraglutide NDA was submitted and the complete final study report has not yet been submitted to the Agency.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: NA  
Study/Clinical trial Completion Date: NA  
Final Report Submission Date: 02/26/2010  
Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Sufficient information in original NDA review to permit approval recommendation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A synopsis of trial 1797 submitted to the Agency suggests liraglutide is more efficacious than exenatide, the only currently approved GLP-1 agonist. However, the Sponsor did not submit full safety data so that a risk-benefit analysis of liraglutide vs. exenatide could be conducted, i.e. safety of liraglutide vs. exenatide was not evaluated in the original application review. This recently completed study will provide some comparative safety information on serious risks of hypoglycemia, pancreatitis, and hypersensitivity reactions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The complete final study report for the recently completed randomized, controlled phase 3 trial (1797) comparing the efficacy and safety of liraglutide to exenatide (currently the only FDA-approved GLP-1 analog).

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
Complete final study report for Study 1797

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  - Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)

---

  - Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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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PMR/PMC Schedule Milestones: Final protocol Submission Date: 03/14/2010  
Study/Clinical trial Completion Date: 09/14/2015  
Final Report Submission Date: 04/30/2016  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Meta-analysis of the combined Phase 2 and Phase 3 premarketing clinical trials of VICTOZA (liraglutide) did not demonstrate an overall increased risk of major adverse cardiovascular events (MACEs). However, the population studied had low baseline cardiovascular risk; the program was not prospectively designed to assess cardiovascular risk; few MACEs occurred; there was some discordance in subgroup analyses; and the duration of blinded controlled study was not sufficient to address the risk definitively.

Liraglutide causes C-cell tumors in two animal species, in both genders, at clinically relevant exposures, in a dose-dependent and time-dependent manner. Cases of medullary thyroid carcinoma (human C-cell cancer) were not seen in clinical trials, but the duration of blinded controlled study was not adequate to assess the risk fully in the premarketing setting. Calcitonin, a biomarker for medullary thyroid carcinoma, is to be measured in the cardiovascular outcomes trial.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry entitled "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". This trial is intended to demonstrate that VICTOZA (liraglutide) does not increase the risk of major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death).

The sponsor has already provided sufficient evidence that liraglutide does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded unacceptable cardiovascular risk. Therefore, consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with liraglutide to that observed in the control group is less than 1.3.

Secondary objectives and adverse events of interest will include an assessment of the long-term effects of liraglutide on calcitonin levels, pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms. These are adverse events of interest based on data from the liraglutide trials or on data from pharmacologically-related products.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blinded, placebo-controlled cardiovascular outcomes trial to be conducted in 9000 patients with type 2 diabetes and increased cardiovascular risk. The primary endpoint will be the first occurrence of cardiovascular death, nonfatal myocardial infarction or stroke. The trial will be event-driven, continuing until a sufficient number of events from the primary endpoint composite has occurred, in order for the trial to have adequate power to rule out an increase in risk of 30% for the primary endpoint. The trial will also have a minimum duration of follow-up of 42 months after randomization for each patient. Serum calcitonin will be measured at baseline; at months 3, 6, 12, 18, 24, 36, 48 and 60; and at end of treatment. Patients with elevated calcitonin will undergo evaluation by an independent calcitonin data monitoring committee, and will be followed until resolution of the elevated calcitonin. In addition to cardiovascular events of interest, all cases of pancreatitis and neoplasms will be adjudicated.

Required

- Observational pharmacoepidemiologic study  
 Registry studies

*Continuation of Question 4*

- Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)

- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)

---

  - Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22341

ORIG-1

NOVO NORDISK  
INC

VICTOZA (LIRAGLUTIDE)

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

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/s/

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AMY G EGAN  
01/21/2010



NDA 022341

**REMS NOTIFICATION LETTER**

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 New Drug Application (NDA) submitted May 23, 2008 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VICTOZA (liraglutide) Injection.

We also refer to your July 8, 2009 submission which contained your proposed Risk Evaluation and Mitigation Strategy (REMS) which consisted of a Medication Guide and a timetable for submission of assessments of the REMS. After reviewing this submission, we have determined that a revision to your proposed REMS is necessary.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for VICTOZA (liraglutide) to ensure that the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing pancreatitis.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that VICTOZA (liraglutide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of VICTOZA (liraglutide). FDA has determined that VICTOZA (liraglutide) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use VICTOZA

(liraglutide). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed VICTOZA (liraglutide).

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe VICTOZA (liraglutide) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about labeling for two years from the date of approval, with emphasis on important product WARNINGS AND PRECAUTIONS including the potential risk of medullary thyroid tumors and the risk of pancreatitis, including necrotizing pancreatitis, and also appropriate patient selection.

The communication plan must include, at minimum, the following:

1. A Dear Healthcare Provider Letter that contains the FDA-approved labeling, which addresses the potential risk of medullary thyroid tumors and the risk of pancreatitis, and appropriate patient selection. This should be mailed within 60 days of product launch.
2. A Direct Mail Letter containing the information included in the Dear Healthcare Provider Letter, but sent annually for the next three years to all prescribers who are likely to prescribe VICTOZA (liraglutide).
3. Highlighted Information for Prescribers to be distributed by Novo Nordisk representatives during the first discussion of the product with all healthcare providers visited during the first six months after product launch. This information will also need to be sent with the Direct Mail Letter.
4. A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the letters will be directed. This should be inclusive of prescribers who are likely to prescribe VICTOZA (liraglutide).
5. All the above components of the Communication Plan as well as the professional labeling must be available via a REMS specific link on the VICTOZA website. The Medication Guide, the Highlighted Information for Prescribers, and the professional labeling must also be available via hardcopy from Novo Nordisk sales specialists, through Novo Nordisk's medical information department, and by calling The Novo Nordisk Answers Center.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than at 1 year, at 2 years, at 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval

covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for VICTOZA (liraglutide). Additionally, all relevant proposed REMS materials including the Dear Healthcare Provider letter, Direct Mail letter, and Highlighted Information for Prescribers should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include, but is not limited to, the following:

- A. Evaluation of patients’ understanding of the serious risks of Victoza (liraglutide [rDNA origin])
- B. Evaluation of healthcare providers’ understanding of the serious risks of Victoza (liraglutide [rDNA origin]).
- C. An assessment of healthcare providers’ awareness of:
  - a. appropriate patient population characteristics, and
  - b. the potential risk for medullary thyroid carcinoma
  - c. the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
- D. Evaluation of healthcare providers’ identification and treatment of:
  - a. medullary thyroid carcinoma after initiation of Victoza (liraglutide [rDNA origin])
  - b. acute pancreatitis after initiation of Victoza (liraglutide [rDNA origin])
- E. Evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed
- F. An assessment of the number of Victoza (liraglutide [rDNA origin]) prescribers identified to receive the Dear Health Care Provider (DHCP) Letter and the number of DHCP letters mailed
- G. An assessment of the percentage of targeted physicians who are presented with the Highlighted Information for Prescribers via Sales Specialists or medical information department

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS with the elements listed above.

Prominently identify the modified proposed REMS submission and subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022341  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

**IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT JOHN BISHAI, PH.D.,  
REGULATORY PROJECT MANAGER, AT (301) 796-1311.**

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

## **APPENDIX A: REMS TEMPLATE**

*If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.*

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL(S):**

List the goals and objectives of the REMS.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide or PPI**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

##### **B. Communication Plan**

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

##### **C. Elements To Assure Safe Use**

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:* List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

#### **E. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than at 1 year, at 2 years, at 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, at 1 year, at 2 years, at 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

## **APPENDIX B: SUPPORTING DOCUMENT**

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information



Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22341

GI-1

NOVO NORDISK  
INC

VICTOZA (LIRAGLUTIDE)

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

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/s/

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MARY H PARKS  
12/21/2009

NDA 22,341

**GENERAL ADVICE**

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

We also refer to your September 24, 2009 email which provided details to your proposed cardiovascular trial entitled "Liraglutide Effect and Action in Diabetes (LEADER): Evaluation of Cardiovascular Outcome Results." We have reviewed the referenced material and have the following additional requests and comments pertaining to the trial design. Please provide a written response.

1. Currently, you are only measuring serum calcitonin as a biomarker for medullary thyroid carcinoma. Include measurement of other potential biomarkers for medullary thyroid carcinoma (calcitonin gene-related peptide, pro-calcitonin, carcinoembryonic antigen) in your cardiovascular trial.
2. It is unclear whether you are using the Division's draft definitions for cardiovascular events. If you are planning to use alternate definitions, include the definitions you are planning to use, together with a tracked version showing where your definitions differ from the Division's draft definitions.
3. Renal impairment is an important long-term complication of diabetes. In addition, there have been postmarketing reports of worsened renal function in Byetta-treated patients. Therefore, you should ensure that, in this cardiovascular trial, there are a minimum of 200 patients with moderate renal impairment who are treated with liraglutide for at least 1 year and a minimum of 100 patients with severe renal impairment who are treated with liraglutide for at least 1 year.
4. For calcitonin monitoring, you state "Subjects who demonstrate a calcitonin level  $>2x$  upper normal range at end of trial and who had levels  $<LLOQ$  at screening will be evaluated approximately 4 weeks post drug discontinuation." This should be revised so that patients are evaluated if baseline serum calcitonin is below the upper limit of normal (ULN) and the last serum calcitonin is  $>2x$  ULN.
5. Immunogenicity has not been adequately assessed in the clinical development program. Anti-drug antibody formation with documented cross-reactivity to endogenous GLP-1

carries a potential risk of inactivation of the native protein and antigen-antibody complex mediated disease. Therefore, you are required to evaluate the rate of anti-liraglutide antibody formation and potential related adverse events after long-term, repeat dosing with liraglutide. The assessment of immunogenicity may be performed in a subset of patients in this cardiovascular trial or as a separate trial. The trial should sample antibody levels at time intervals sufficiently separated from dosing to avoid interference from the drug with the antibody assay. Antibody levels should be assessed at multiple timepoints during the course of the trial to provide information on the kinetics of anti-drug antibody formation. The number of patients sampled should take into account the overall rate of seroconversion (~10%), as well as the rates of seroconversion for neutralizing antibodies (~1-2%) and cross-reactive antibodies (~5%) observed in the Phase 3 trials. In addition to antibody levels, the immunogenicity assessment should include ongoing screening for laboratory parameters and adverse events related to inactivation of the native protein and possible antibody complex mediated disease (e.g. cutaneous and musculoskeletal manifestations, complement levels, hepatic transaminases, and renal function).

If you have any questions, call John Bishai Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22341

-----  
ORIG-1

-----  
NOVO NORDISK  
INC

-----  
VICTOZA (LIRAGLUTIDE)

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

MARY H PARKS  
12/03/2009

**NDA Amendment - Labeling**



December 1, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza (liraglutide [rDNA origin] injection)  
NDA Amendment: Response to FDA Comments on November 25<sup>th</sup> Draft  
Medication Guide**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments on the draft Medication Guide received in an e-mail from FDA Project Manager, John Bishai on November 25, 2009.

All FDA's recommendations have been reviewed, and, in response, we are returning:

- WORD version with tracked changes to indicate Novo Nordisk's acceptances of FDA requests, as well as proposed revisions.
- clean WORD version.
- PDF which shows how the Medication Guide will be laid out when printed and packaged in the carton with the pen.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5817 created on November 29, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.

Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mlho@novonordisk.com  
Date: 2009.12.01 08:36:57 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

**NDA Amendment - Labeling**



November 25, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza (liraglutide [rDNA origin] injection)  
NDA Amendment: Response to FDA Comments on November 23<sup>rd</sup> Draft Pen  
Instructions for Use**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments on the draft pen Instructions for Use received in an e-mail from FDA Project Manager, John Bishai on November 23, 2009.

All FDA's recommendations have been reviewed, and, in response, we are returning:

- WORD version with tracked changes to indicate Novo Nordisk's acceptances of FDA requests, as well as proposed revisions.
- clean WORD version.
- PDF which shows how the Instructions for Use will be laid out when printed and packaged in the carton with the pen.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5810 created on November 22, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.

Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson  
on behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf  
of Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.25 08:54:19 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
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www.novonordisk-us.com



NDA Amendment



November 23, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA General Advice Letter dated November 13, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza® (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the November 13, 2009 General Advice Letter from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is responding to FDA's comments on our Postmarketing Requirement studies. Please note that a complete response to some of these questions/comments will need to await the final protocols. We believe that the current responses provide a clear direction based on your comments for the development of final protocols that will be consistent with the intent of the Agency to gather additional safety data on liraglutide.

Also, as requested, we are providing updated timelines for each of the studies:

Cancer Registry Timelines\*

b(4)

Final Protocol Submitted to FDA: \_\_\_\_\_

Study Completion: . \_\_\_\_\_

Final Study Report Submitted to FDA: \_\_\_\_\_

\*Please note this timeline reflects our proposal for registry duration of 15 years. Please see the attached document which provides a rationale for this timeline.

Epidemiological Study Timelines

**b(4)**

Final Protocol Submitted to FDA: \_\_\_\_\_

Study Completion: \_\_\_\_\_

Final Study Report Submitted to FDA: \_\_\_\_\_

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5806 created on November 18, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.23 16:48:09 -05'00'

Mary Ann McElligott, Ph.D.

Associate Vice President, Regulatory Affairs

Novo Nordisk Inc.

609-987-5831 (direct)

[mamc@novonordisk.com](mailto:mamc@novonordisk.com)

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

**NDA Amendment**



November 23, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA request for information dated  
November 12, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza® (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the November 12, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information on the case of hepatic failure as an Amendment to NDA 22-341. Please note an initial and follow-up MedWatch reports for this case was provided to the Agency on November 9 and November 18, 2009 to IND 61,040 (Sequence 393 and 399). The follow-up report is included again herein for ease of reference. If we obtain any additional follow-up information on this case it will be promptly forwarded to the Agency.

The second part of this request, information on a postmarketing case from Germany, will be provided to the Agency as soon as it is available.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5806 created on November 18, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

**Novo Nordisk Inc.**  
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609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
Ann McElligott

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DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.23 09:24:19 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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[mamc@novonordisk.com](mailto:mamc@novonordisk.com)

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
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[www.novonordisk-us.com](http://www.novonordisk-us.com)

## NDA Amendment - Labeling



November 16, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza (liraglutide [rDNA origin] injection)  
NDA Amendment: Response to FDA Comments on November 12<sup>th</sup> Draft  
Physician Insert and November 13<sup>th</sup> Draft Carton and  
Container Labels**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments received in e-mails from FDA Project Manager, John Bishai for:

- Draft Physician Insert received on November 12, 2009
- Draft Carton and Container Labels received on November 13, 2009

### **Draft Physician Insert**

All FDA's recommendations have been reviewed, and, in response, we are returning the draft Physician Insert with tracked changes to indicate Novo Nordisk's acceptances of FDA requests, as well as proposed revisions. Novo Nordisk's proposed revisions in the enclosed draft label are primarily data focused; we are proposing these revisions based on FDA feedback and also to ensure clarity on the label.

Novo Nordisk has also noted areas in the proposed Physician Insert where we would appreciate the opportunity to discuss further with the Division in a teleconference as we believe that this approach will allow more efficient resolution of outstanding questions. We are available this week for the teleconference and would appreciate the Division's timely scheduling.

### **Draft Carton and Container Labels**

FDA's comments are provided below in italics followed by Novo Nordisk's responses.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

# 2 Page(s) Withheld

       Trade Secret / Confidential (b4)

  √   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

This submission is being provided electronically (approximately 6 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5799 created on November 11, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson  
on behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf  
of Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.16 13:08:56 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
[mamc@novonordisk.com](mailto:mamc@novonordisk.com)

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)



NDA 22-341

**GENERAL ADVICE**

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 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

We also refer to your July 8, 2009 submission, containing your Risk Evaluation and Mitigation Strategies (REMS) supporting document and the following postmarketing studies.

1. A cancer registry protocol entitled "Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry".
2. An epidemiological study entitled "A Health Care Database study using i3 Aperio to Evaluate Safety of liraglutide".

The review of your REMS is ongoing. We have completed the review of the two postmarketing studies described above and have the following comments and requests.

**Cancer registry comments:**

**1. Contractor and staff not identified and previous experience with similar studies not provided**

The protocol should include the name of the contractor and staff credentials, and should mention any previous experience with similar studies.

**2. Participation of cancer registries and comprehensive cancer center registries**

The study's objective, to define the incidence of medullary thyroid cancer (MTC) in the United States, will be seriously compromised if there is poor participation of cancer registries and comprehensive cancer center registries. The protocol states that cancer registries that have at least 10 reported cases of MTC per year and meet the North American Association of Central Cancer Registries (NAACCR) standards for data collection and timeliness will be invited to participate. The protocol also states that in areas where a population-based registry is unable or unwilling to participate, comprehensive cancer center registries may be directly invited to participate. At least 14 states will be asked to



participate in the MTC case series registry, representing a total of 1789 (75%) of the 2375 cases reported historically from 2001-2005. If even a few of the 14 states refuse participation, the rate might drop to around 50%.

Clarify the basis for only targeting sites that represent at most 75% of MTC cases.

Of note, a similar “case series study established to monitor at least 40% of osteosarcomas occurring annually in men and women older than 40 years old who reside in the United States” (1) to detect an association of osteosarcoma with teripatide (Forteo), apparently has not detected any cases, although two cases of osteosarcoma following teripatide exposure have been reported in the medical literature (1, 2). The first case involved a “postmenopausal woman in her 70s with a complex past medical history” initially reported to a Lilly sales representative (2). The second teripatide-exposed osteosarcoma case was a 67-year-old man with a history of radiation therapy who used teripatide two months before his diagnosis of osteosarcoma, according to clinicians at the University of Texas M.D. Anderson Cancer Center (1). The two cases were among the “more than 430,000 persons who have received teripatide for treatment of severe osteoporosis” (1).

The protocol does not state whether similar case series registries have been undertaken previously using NAACCR data, and what the participation rate was or can be expected to be. This information should be included in the protocol. If this is the first time that the NAACCR is engaging in this type of study, this should be stated.

Sensitivity analyses showing various participation rates should be presented.

The protocol states that compensation will be provided to each registry for the work involved in identifying and recruiting patients and physicians. The question arises whether the compensation will be incentive enough to enhance cancer registry participation rates. Pilot testing might be performed to determine if the amount offered will be enough to enhance participation.

### **3. Participation of patients**

This study and its objectives will be significantly compromised if there is poor enrollment/participation of patients. Many studies do not achieve desired participation rates when patients are contacted for consent to enroll in a study and to provide and release personal medical information over the telephone. The protocol should state the proposed number of telephone call-back attempts (with varying times of day) that will be made before the patient is counted as a non-respondent.

The protocol should state the expected range of patient participation rates and the resulting sample sizes. Patients will be offered an incentive of \$25 to complete the telephone interview. Pilot testing might be performed to determine if the amount offered is enough to enhance participation.

### **4. Participation of physicians**

In situations where a state or regional cancer registry is unable to directly contact a patient, the cancer registry staff will ask the patient’s physician identified in their records to provide the desired patient information for the MTC case series registry or to directly

recruit the patient. If physicians fail to recruit patients or provide patient information, the study will be seriously compromised.

When allowed by the cancer reporting registry, physicians will be contacted to complete a data collection form for any patient who is deceased. The protocol should state what proportion of cancer registries will allow this contact, and provide a range for the expected participation rate in completing the data collection form.

**5. Sample size, missing reports, and reporting to AERS**

Sample size might be low because, as stated above, it will depend on the joint participation of cancer registries, physicians, and patients. Sensitivity analyses showing various assumptions for participation rates, relative risks, and latency periods for the development of MTC should have been presented.

Because MTC is rare, missing even a couple of cases of MTC in liraglutide-exposed patients could lead to serious under-ascertainment of risk.

Missing cases in the MTC case series registry might be supplemented by timely reporting of MTC in liraglutide-exposed patients to the FDA's Adverse Event Reporting System (AERS). Consequently, the product information and the Medication Guide should prominently display the FDA's MedWatch contact information.

**6. Possible difficulty in detecting a change in MTC incidence and interpretation of any change**

If liraglutide use is relatively low, it may not be possible to detect a change in MTC incidence even if the drug causes MTC.

Furthermore, if the national (background) incidence of MTC changes during the study period compared with the baseline period, it may be difficult to determine that the change is due to liraglutide. The protocol should acknowledge problems with the interpretation of ecological data.

**7. Lag time between diagnosis and cancer registry registration**

From data accumulated by the NAACCR, the protocol should state what the average lag time is between the date of diagnosis and the reporting of MTC to the cancer registry.

**8. Detection of double counting of patients**

Since there might be overlap between data accumulated by NAACCR and comprehensive cancer center registries, the cancer registry and Study Coordinating Center staffs should be aware of, and try to avoid, any double counting of patients.

**9. Identifying deceased patients and obtaining exposure information**

The protocol should state if patients diagnosed with MTC at death are included in the cancer registries. If possible, the proportion of patients diagnosed at death with MTC should be provided.

Obtaining exposure information for anti-diabetic medications for deceased patients may be difficult, and misclassification of exposure is a potential problem.

#### **10. Collecting additional data on thyroid conditions**

The Study Coordinating Center will collect additional demographic data, medical history, and exposure information by telephoning the patient or his/her proxy. In addition to the list of information requested, history of other thyroid conditions should be added including hypothyroidism and hyperthyroidism. Weight and height information should also be added to the list of lifestyle factors.

The protocol should specifically state if all anti-diabetic medications including insulin will be requested from the patient and his/her proxy.

The protocol should state the relevant time period for data collection (e.g., antidiabetic use at any point in the patient's life, use in the past five years, etc.).

#### **11. Use of proxies to obtain data and probability of missing information**

Unless the proxy is the spouse of the patient with MTC, he/she is unlikely to know the answers for much of the information requested. Consequently, use of proxies is likely to be associated with more missing and lower quality data.

#### **12. Interpretation of data due to absence of controls**

Because no control data will be collected, causality assessment will likely be problematic. The Data Monitoring Committee, in consultation with Novo Nordisk and the FDA, will decide if a case-control study is warranted. In anticipation of the need for such a study, the protocol should state what controls might be appropriate.

#### **13. Representativeness of data**

Because the data on MTC will not be a total count of cases nor a scientific sample from cancer registries, they may not be a reliable estimate of the incidence of MTC in the United States. The protocol should acknowledge this. Performing demographic comparisons between cases included and not included may help determine the representativeness of those included.

#### **14. Registry duration**

Because MTC typically has a long latency, lengthen the duration of the registry from 10 years to 20 years. Include your plans for interim analyses during this 20 year time period.

#### **15. Enlisting assistance from endocrine professional associations**

Most patients with MTC are seen by endocrinologists and endocrine surgeons. In addition, patients are more likely to be willing to share their information if their treating physician encourages participation in the registry. Therefore, you should enlist the help of endocrine professional associations to achieve these goals. Explore this possibility further with these professional associations and submit a proposal to FDA.

## 16. Publication of data

The protocol states that a final study report will be provided to the FDA within 6 months of the completion of the study.

Novo Nordisk and \_\_\_\_\_ should commit to a plan to publish the data to make publicly available more information on MTC incidence and potential etiology as well as procedural and methodological issues involved in setting up a case series registry for a rare event.

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### Epidemiological Study Comments:

#### 1. Interpretation of results when comparing only drugs within a class

To determine a drug's unique profile of adverse events, it is useful not only to compare drugs within the same therapeutic class, but also to compare those that are not within the same therapeutic class. Drugs within the same therapeutic class often have similar adverse event profiles and, therefore, no important adverse event differences are found; however, differences are more likely found when comparing drugs that are not in the same therapeutic class. Therefore, one cannot conclude that a drug does not have an adverse event based on a comparison with other drugs in the same class, but only that no large differences exist among the drugs in frequencies of the adverse event. As a result, it would be useful if the i3 Aperio system also allowed for comparison of liraglutide with other chronically used drugs outside its therapeutic class (e.g., antihypertensives or cholesterol-lowering drugs).

#### 2. Rule-out or provisional diagnoses and misclassification of outcome

While i3 Aperio might be useful as a safety surveillance tool, it would not provide definitive results because it is expected that a large proportion of diagnoses will be "rule out" or provisional diagnoses with misclassification of outcomes. A recent study by i3 Drug Safety staff that concerned validation by medical records of acute pancreatitis diagnosis codes indicated that the positive predictive value was 49% (3). In the i3 Aperio study, the primary outcome of interest, thyroid cancer, and most secondary outcomes including pancreatitis, myocardial infarction, ischemic heart disease, stroke, heart failure, retinopathy, nephropathy, neuropathy, and peripheral vascular disease would require validation by medical records.

#### 3. Absence of ICD code for medullary thyroid cancer

There is no International Classification of Diseases (ICD) code specific for medullary thyroid cancer. Consequently, any thyroid cancers that are identified in this study would require that medical and histological records be obtained to identify the type of cancer. This should be stated explicitly in the protocol. Please note that some practitioners also use diagnostic codes for calcitonin disorders to identify patients with medullary thyroid cancer.

#### 4. "Thyroid events" as an outcome

The protocol should specify what “thyroid events,” in addition to thyroid cancer, are of interest and would be analyzed using i3 Aperio.

#### 5. Sample size and statistical power

The protocol states that “Approximately 5,000 active subjects exposed to liraglutide in the database per year and approximately 25,000 subjects exposed to liraglutide in 5 years are expected.” Subjects exposed to metformin, exenatide, sulfonylureas, sitagliptin, rosiglitazone, and pioglitazone are already in the database. Based on propensity score matching, the same numbers exposed to these comparators will be included in 1:1 ratio. So the total sample size will be approximately 150,000 in 5 years.”

The protocol does not provide any basis for its estimation of 5,000 subjects exposed to liraglutide per year, 25,000 over 5 years, and the sample size for comparator anti-diabetic medications of 150,000 in 5 years. The company should provide some basis for its exposure estimates. Also, it should provide estimates of the range of exposure to liraglutide and perform calculations using these ranges to estimate statistical power for the ability to detect differences in drugs for thyroid cancer incidence and other key endpoints of interest. Based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data for 2002-2006 (4), the age-adjusted annual incidence rate of invasive thyroid cancer for all ages, both sexes, and all races was 9.6 per 100,000 population, and for individuals < 65 years old, it was 8.7 per 100,000 population, or about 1 per 11,500 population (4). Furthermore, medullary thyroid cancer, the human equivalent of C-cell carcinoma in rodents and the greatest concern because of its case-fatality rate, accounts for a fairly small proportion of thyroid cancer overall, estimated at 1.6% to 5%. According to a separate protocol submitted by Novo Nordisk concerning active surveillance of medullary thyroid cancer with a personal communication from the North American Association of Central Cancer Registries, the age-adjusted rate in the United States for the period 2001 through 2005 was 0.2 per 100,000. Consequently, unless exposure to liraglutide and the risk of thyroid cancer in liraglutide-exposed patients is high and the latency period for thyroid cancer is relatively short, very few cases of thyroid cancer and probably no cases of medullary thyroid cancer will be identified over the five-year study period.

Besides thyroid cancer, other rare outcomes also would be unlikely to be detected.

#### 6. Representativeness and generalizability of the findings

Since i3 Aperio uses data from the \_\_\_\_\_, database of medical claims from mostly employed individuals who are generally ≤ 65 years of age, the findings would be most applicable to this group.

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#### 7. Lack of complete mortality data

Deaths that occur in a hospital affiliated with \_\_\_\_\_ would result in a claim in the database; however, if a death occurred outside of an affiliated hospital (as is often the case) and without the plan’s coverage, no claim would be filed and neither the fact of death nor the cause of death would be identified in the \_\_\_\_\_ or in the i3 Aperio systems. The sponsor might be able to remedy this by accessing the National Death Index of the

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National Center for Health Statistics to identify the fact and causes of death of included patients, especially those who are lost to follow-up.

#### **8. Inclusion/exclusion of patients taking insulin**

Although the protocol states that patients with type 2 diabetes who are  $\geq 18$  years of age and treated with one or more oral antidiabetic drugs for the last 3 months and satisfy the enrollment criteria can be included in the study, it does not specify if patients who use insulin concomitantly with the study drugs will be included or excluded. A statement should be made regarding whether concomitant insulin will be an inclusion or exclusion criterion, and, if included, how concomitant insulin use data will be analyzed (e.g., by stratification or adjustment).

#### **9. Selection bias and injectable antidiabetic agents**

In analyses, liraglutide, an injectable antidiabetic agent, will be compared 1:1 with mostly oral antidiabetic agents. Since it's likely that persons using an injectable product have more serious diabetes, analyses should be presented to show that propensity score matching takes account of increased severity of diabetes in liraglutide-exposed patients by comparing the drugs at baseline and after propensity score matching. Also, the analyses should provide the number of patients who were not able to be matched and were excluded from the analyses.

#### **10. "Intent-to-treat analysis" and exposure misclassification**

The protocol states that "Although patients may switch from one drug to the other after the first dispensing of a drug of interest, the principle of intent-to-treat analysis will be followed, such that each patient is assigned to a cohort according to the first dispensing of a drug of interest." Further it states that "The two cohorts (liraglutide and comparator initiators) are followed indefinitely as long as the patient is an active health plan member, regardless of persistency in antidiabetic drug and switching between different antidiabetic drugs." However, because discontinuation and switching of antidiabetic agents is expected, exposure misclassification over time is likely, resulting in problems with interpretation of positive findings.

The protocol should discuss the rationale for an intent-to-treat analysis as compared with a time-to-event analysis that takes discontinuation, switching, and duration of medication use into account.

#### **11. Possible inability to obtain medical records for validation purposes**

Although the protocol states that i3 Drug Safety staff has been successful in obtaining medical records to validate diagnoses, it does not state what their usual success rate is. This should be stated because in some studies the rate of obtaining medical records has been as low as 50%.

#### **12. Lack of information on testing for balance following propensity score matching**

The i3 Aperio system should show statistically significant differences between liraglutide and the comparator drug at baseline and after propensity score matching to show the effect of the matching process. The number of individuals who could not be matched and remain outside of the analyses should be provided.

### **13. Missing information for potentially important confounders**

The protocol acknowledges that “given the potentially wide range of outcomes of interest to be evaluated, there may be important confounders for certain outcomes that may not be measured and adequately controlled for in the design and analysis.” Important confounders that would be likely missing over time in claims data include cigarette smoking, body mass index, alcohol use, illegal drug use, non-prescription drug use, etc.

### **14. Latency of claims data**

While pharmacy claims data are included in the database within about six weeks of payment of the underlying claim and laboratory tests are generally added within six weeks of the test, six months is required to capture 95% of medical claims data.

### **15. Difficulty interpreting multiple tests of significance**

Because a wide range of outcomes will be compared between liraglutide and comparator drugs, a number of outcomes may achieve statistical significance based on chance alone. Consequently, acknowledgment of this issue should be made in the protocol’s methods section.

### **16. Hypersensitivity reactions**

Include an endpoint for serious hypersensitivity reactions.

### **17. “Track record” of the i3 Aperio database**

In general, after several years of operation, the i3 Aperio database is not known for its ability to identify new serious adverse drug events. Using i3 Aperio as a search term in PubMed, there are only two published studies in which i3 Aperio was used (5,6), and in both studies adverse events were not identified or confirmed. Epidemiologists who have used the i3 Aperio database at the FDA for exploratory analyses stated that they have not found it to be particularly useful in this respect.

### **18. Publication of Data and Submission of Full Electronic Datasets**

The protocol should be published or publically posted prior to initiation of the study. The final statistical analysis plan should be submitted prior to analysis of any data. The study report should be published. When the study report is submitted to the FDA, full electronic datasets should also be submitted.

**Other Comments:** When you submit revised proposals for these postmarketing requirements, include updated timelines for each study that include (a) the date by when the finalized protocol

will be submitted to FDA, (b) the date by when the studies will be completed, and (c) the date by when the complete study reports will be submitted to FDA.

If you have any questions, call John Bishai, Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



## REFERENCES

1. Subbiah V, Madsen VS, Raymond AK, Benjamin RS, Ludwig JA. Of mice and men: divergent risks of teripatide-induced osteosarcoma. *Osteoporos Int* 2009; July 14 [Epub ahead of print], DOI 10.1007/s00198-009-1004-0.
2. Harper KD, Krege JH, Marcus R, Mitlak BH. Comments on Initial experience with teripatide in the United States. *Curr Med Res Opin* 2006;22(10):1927.
3. Dore DD, Hoffman C, Quinn SG, Chaudhry S, Seeger JD. Positive predictive value (PPV) of commercial health insurance claims data for identifying acute pancreatitis (AP) in patients with diabetes mellitus (DM). Abstracts of the 25<sup>th</sup> ICPE 2009. *Pharmacoepidemiol and Drug Saf* 2009;18:S1-S273, DOI:10.1002/pds.
4. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlander N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2006/](http://seer.cancer.gov/csr/1975_2006/) based on November 2008 SEER data submission, posted to the SEER website, 2009.
5. Strombom I, Wernicke JF, Seeger J, D'Souza DN, Acharya N. Hepatic effects of duloxetine-III: Analysis of hepatic events using external data sources. *Curr Drug Safety* 2008;3:154-162.
6. Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Research and Opinion* 2009;25:1019-1027.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H PARKS  
11/13/2009



NDA 22-341

**GENERAL ADVICE**

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 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

We also refer to your September 30, 2009 submission, containing your revised pen and carton labeling.

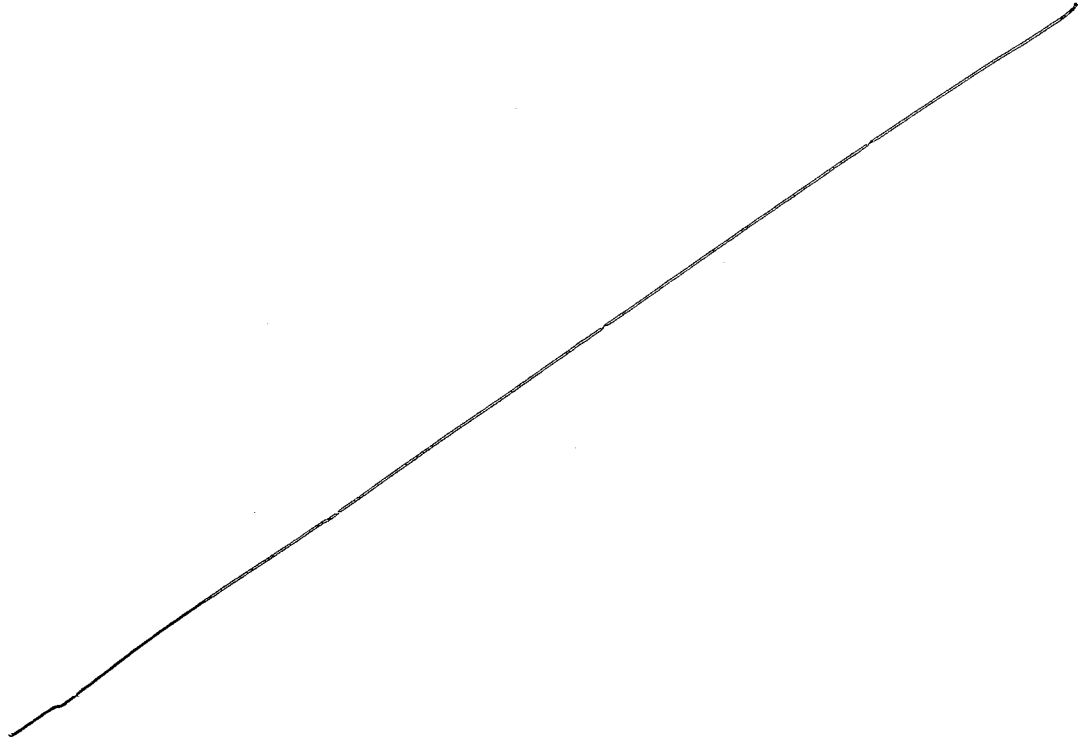
We have reviewed the referenced material and have the following comments.

**Pen Label (Retail and Physician Samples)**

1. Include a statement on the principle display panel that the pen is for single patient use only.
2. Include the total drug content statement, '18 mg/3 mL (6 mg/mL)' following the dosage form statement in accordance with USP requirements.
3. Revise the dose statement, '0.6/1.2/1.8 mg' appearing to the right of the proprietary name to read, 'Pen delivers doses of 0.6 mg, 1.2 mg or 1.8 mg', and relocate this statement to appear on the principle display panel after the total drug content and concentration statement. As currently presented, '0.6/1.2/1.8 mg' lacks the units of measure following each dose and may be misinterpreted to mean that the pen is a combination product that contains three different active ingredients.

b(4)

**Carton Labeling**



**b(4)**

If you have any questions, call John Bishai, Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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/s/  
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MARY H PARKS  
11/13/2009

**NDA Amendment**



November 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA Advice Letter of October 7, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to your October 7, 2009 Advice Letter on our proposed cardiovascular study entitled “Liraglutide Effect and Action in Diabetes (LEADER): Evaluation of Cardiovascular Outcome Results.”

We appreciate your comments and the recommendations you provided after review of the draft protocol. For clarity and to ensure we are appropriately addressing your comments and incorporating your recommendations, we are providing responses to the items included in your advice letter in the attached document. We are hoping to finalize the protocol shortly in order to begin study start-up activities and would welcome any additional feedback.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5796 created on November 8, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
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609-987-5800 phone  
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NDA Amendment



November 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA request for information dated  
October 15, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza® (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 15, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. Please note a follow-up MedWatch report for this case was provided to the Agency on November 5, 2009 to IND 61,040 (Sequence 390). The information in that MedWatch is summarized in this response. If we obtain any follow-up information on this case it will be promptly forwarded to the Agency.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5796 created on November 8, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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Signed by  
Michelle Thompson  
NOVO NORDISK I.  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson  
on behalf of Mary Ann McElligott  
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of Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.11 15:57:45 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
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Princeton, NJ 08540  
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**NDA Amendment - Labeling**



November 3, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza (liraglutide [rDNA origin] injection)  
NDA Amendment: Response to FDA Comments on October 29<sup>th</sup> Draft Physician  
Insert**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments on the draft Physician Insert received in your e-mail of October 29, 2009.

All FDA's recommendations have been reviewed, and, in response, we are returning the draft Physician Insert with tracked changes to indicate our acceptance of FDA requests, as well as proposed revisions. We acknowledge FDA's comments regarding some discrepancies in the numbers being reported. In order to be consistent with the Physician Insert and to ensure accuracy of incidence rates, we have used information provided up to the 120 Day Safety Update (cut-off May 30, 2008).

Novo Nordisk would appreciate the opportunity to discuss the Physician Insert further with the Division in a teleconference as we believe that this approach will allow more efficient resolution of outstanding questions. We also look forward to discussing other outstanding items with the Division including PMR/PMC and REMS.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5789 created on November 1, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

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Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.11.03 11:16:53 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
[mamc@novonordisk.com](mailto:mamc@novonordisk.com)

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Pulmonary and Allergy**  
Sandy Barnes  
OND/ODEII/DPA  
sandy.barnes@fda.hhs.gov  
WO22 RM3306/ Phone: X6-1174

FROM (Name, Office/Division, and Phone Number of Requestor): **John Bishai**  
Regulatory Project Manager  
DMEP, HFD-510, Phone: 796-1311

DATE 10/28/09	IND NO.	NDA NO. 22,341	TYPE OF DOCUMENT NDA original submission	DATE OF DOCUMENT May 23, 2008
NAME OF DRUG Victoza (Liraglutide)		PRIORITY CONSIDERATION YES	CLASSIFICATION OF DRUG GLP-1- Treatment of Diabetes	DESIRED COMPLETION DATE ASAP

NAME OF FIRM: **Novo Nordisk**

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |   |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### II. BIOMETRICS

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|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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#### IV. DRUG SAFETY

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|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Patients treated with liraglutide can develop antibodies to liraglutide and some nonclinical data demonstrate that such antibodies cross react with native GLP-1. Please evaluate the clinical relevance of antibody formation and what additional studies or monitoring are necessary. (Data will be shortly sent)

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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**This is a representation of an electronic record that was signed  
electronically and this page is the manifestation of the electronic  
signature.**  
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/s/  
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JOHN M BISHAI  
10/28/2009

**NDA Amendment**



October 26, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA request dated October 21, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 21, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5778 created on October 21, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on behalf  
of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
com  
Date: 2009.10.26 13:46:53 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

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Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

**NDA Amendment**



October 21, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Follow-up to FDA Request dated October 2, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 2, 2009 request from FDA Division Director, Dr. Mary Parks and Novo Nordisk's responses dated October 7 and 8, 2009.

At this time, Novo Nordisk is providing additional information on this patient as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5775 created on October 18, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
Ann McElligott

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Ann McElligott, c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.10.21 10:36:49 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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[www.novonordisk-us.com](http://www.novonordisk-us.com)



## REQUEST FOR CONSULTATION

TO (Office/Division): **DDMAC**  
**Division Of Drug Marketing, Advertising And  
 Communication**  
**Sam Skariah**  
**White Oak Office Building 51 (WO51)**  
**Room # 3226, phone: 7-8444**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**John Bishai Ph.D.**  
**Regulatory Project Manager**  
**DMEP, HFD-510, phone #: 6-1311**

DATE October 16, 2009	IND NO.	NDA NO. 22-341	TYPE OF DOCUMENT PI Label Review	DATE OF DOCUMENT September 30, 2009
NAME OF DRUG Victoza (liraglutide)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic agent	DESIRED COMPLETION DATE October 23, 2009

NAME OF FIRM: **Novo Nordisk**

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

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|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### III. BIOPHARMACEUTICS

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|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILTY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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#### IV. DRUG SAFETY

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|---|---|
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|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

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|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the PI which can be found in the DMEP eRoom.  
[http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0\\_cff9](http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_cff9)

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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electronically and this page is the manifestation of the electronic  
signature.**  
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/s/  
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JOHN M BISHAI

10/16/2009

## Bishai, John

---

**From:** Bishai, John  
**Sent:** Wednesday, October 14, 2009 12:16 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** RE: FINAL NDA 22-341 CV LEADER letter.pdf - Adobe Acrobat Professional

Hello Michelle,

In regards to our cardiovascular advice letter which was attached in my October 12th email, we have two more comments to add. They are as follows:

1. Measure serum calcitonin in all patients approximately 1 month after the last dose of study medication. If the end of treatment serum calcitonin value is higher than the baseline serum calcitonin value then you should follow calcitonin periodically off treatment until the calcitonin stabilizes or returns to baseline values.
2. Please clarify the process that will be used to adjudicate pathology results obtained from thyroidectomy.

If you have any questions, please feel free to contact me.

Thanks,  
John

---

**From:** Bishai, John  
**Sent:** Monday, October 12, 2009 12:22 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** FINAL NDA 22-341 CV LEADER letter.pdf - Adobe Acrobat Professional

Hello Michelle,

First, I wanted to apologize for the delay, but as promised please find our cardiovascular recommendations attached. If you have any questions, please feel free to contact me tomorrow as I am out of the office today.

Regards,  
John  
<< File: FINAL NDA 22-341 CV LEADER letter.pdf >>

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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/s/  
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JOHN M BISHAI  
10/14/2009

## Bishai, John

---

**From:** Kaye, Ron D.  
**Sent:** Thursday, August 06, 2009 4:11 PM  
**To:** Bishai, John; Zimliki, Charles L\* (CDRH); Syed, Sajjad H  
**Cc:** Parks, Mary H  
**Subject:** RE: NDA 22-341 Liraglutide

No problem with using this memo for the record. I will keep it in my records as well.

Thanks,  
Ron

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

**From:** Bishai, John  
**Sent:** Thursday, August 06, 2009 4:06 PM  
**To:** Kaye, Ron D.; Zimliki, Charles L\* (CDRH); Syed, Sajjad H  
**Cc:** Parks, Mary H  
**Subject:** RE: NDA 22-341 Liraglutide

Hello Ron,

I wanted to thank you for your quick response, and I'm glad to hear that your review of their on-going study is promising. I will take the liberty of conveying your thoughts to the sponsor, and I will be sure to cc: on the email. In regards to your consult, your email will suffice, so there is no need for an official review as long as you are okay with me archiving this into the records.

Thanks again.  
-John

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

**From:** Kaye, Ron D.  
**Sent:** Thursday, August 06, 2009 3:52 PM  
**To:** Bishai, John; Zimliki, Charles L\* (CDRH); Syed, Sajjad H  
**Cc:** Bishai, John  
**Subject:** RE: NDA 22-341 Liraglutide

John,

If they are following the protocol from Feb 2008 and the results of the study will be consistent with the intent of the protocol, this study is not a bad one. That report should be specific with respect to intended assessments such as "number of use errors" (for example) such that the number is provided as well as a description or characterization of errors.

The questionnaire is incomplete in that it does not capture the nature of the problem, being only a collection of rating scales. The rating scales are OK but for items such as "rate the ease of injection," for example, if the rating were to be low, we would want the participant to be able to briefly describe the nature of the difficulty. Such responses can be elicited directly following the rating item or in a separate set of "open ended" questions. Verbal (written) responses should be collated and presented and reviewed with respect to the objectives of the study and provided along with other results in the study report.

Finally, there were specific modifications to this injector including the label. The study should direct specific inquiry to these modifications with respect to their impact on users. This would not be a large change and could be accomplished by modifying the questionnaire to address the design modifications to include capture of participant responses asking them to describe any aspects of the design that they found confusing or difficult.

Since these comments are relatively brief, feel free to relay them to the manufacturer directly or, if you prefer, I can talk to them.

If you would prefer to receive the above comments in a "consult" form I can provide that but I wanted to give you a quick turnaround on this.

Thanks,

Ron

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

From: Bishai, John [mailto:John.Bishai@fda.hhs.gov]  
Sent: Thursday, August 06, 2009 12:00 PM  
To: Kaye, Ron D.; Zimlik, Charles L\* (CDRH); Syed, Sajjad H  
Cc: Bishai, John  
Subject: NDA 22-341 Liraglutide

Hello,

As per our t-con, I am sending a link to the sponsor's ongoing "HF study." Unfortunately, there is a good chance that this will not qualify as an HF and will more likely be considered a usability study. I would like to take this time to remind you that an interim report will be in house early next week, and I will file it in the same location as this protocol. After looking over this study, please send me any comments you may have or let me know if you would like to set up a teleconference with the sponsor to resolve any issues. Once again, the study is ongoing, and any study design modifications you would like can be done at this time. However, we should inform the sponsor as soon as possible.

Please feel free to contact me if you have any questions.

Thanks,  
John

Please check out this item in the CDER Division of Metabolism and Endocrinology Products eRoom:

CDER Division of Metabolism and Endocrinology Products/ Consults/ Outgoing DMEP Consults/  
Open/ NDA 22-341/ Liraglutide/ Human Factors  
[http://erom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/  
0\\_dbf1](http://erom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_dbf1)

To turn on notification for this item, go to:

[http://erom.fda.gov/eRoomASP/FormDispatcher.asp?Dlg=DlgNotifications&ID=0\\_dbf1  
&Ctxt=.CDER3.CDERDivisionofMetabolismandEndocrinologyProductsConsults.0\\_dbf1](http://erom.fda.gov/eRoomASP/FormDispatcher.asp?Dlg=DlgNotifications&ID=0_dbf1&Ctxt=.CDER3.CDERDivisionofMetabolismandEndocrinologyProductsConsults.0_dbf1)

Application  
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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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/s/  
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JOHN M BISHAI  
10/14/2009

**NDA Amendment**



October 13, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Responses to FDA request for information dated  
October 6, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 6, 2009 request from FDA Division Director, Dr. Mary Parks.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5768 created on October 11, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary Ann  
McElligott

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
com  
Date: 2009.10.13 13:28:05 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
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**NDA Amendment**



October 8, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Responses to FDA request for information dated  
October 8, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 8, 2009 request from FDA Division Director, Dr. Mary Parks.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5761 created on October 4, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

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NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of **Mary**  
**Ann McElligott**

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Date: 2009.10.08 15:17:41 -04'00'

Mary Ann McElligott, Ph.D.  
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Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

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NDA Amendment



October 7, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Responses to FDA request for information dated  
October 2, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the October 2, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5761 created on October 4, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of **Mary Ann McElligott**

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
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NDA 22,341

**GENERAL ADVICE**

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (Liraglutide) Injection.

We also refer to your July 8, 2009 submission in addition to your email, dated September 2, 2009, which contained an update, for your proposed cardiovascular study entitled "Liraglutide Effect and Action in Diabetes ( \_\_\_\_\_ )" **b(4)**

We have reviewed the referenced material and have the following comments and recommendations. Furthermore, we have provided a draft of our current Cardiovascular recommendations.

1. Please also exclude patients with a history of non-familial medullary thyroid carcinoma.
2. Please list hypersensitivity reactions and renal safety as adverse events of interest and include secondary endpoints related to renal safety.
3. Upon reviewing your protocol, it is not clear whether patients with a history of pancreatitis would be enrolled. During enrollment, patients should be questioned about a history of pancreatitis, but a history of pancreatitis should not be used as an exclusion criterion.
4. All liraglutide-treated patients should be force-titrated to 1.8 mg unless there are tolerability issues (i.e., the statement "After randomization, liraglutide or liraglutide placebo will be introduced at a dose of 0.6 mg/day gradually increased to 1.8 mg/day, unless other maximum dose is specified by the locally approved label" should be revised accordingly.
5. Estimate the anticipated number of patients with mild, moderate, and severe end-stage renal disease that you anticipate enrolling in the trial. Present these data in

two ways. One using the Cockcroft-Gault formula and another using the Modification of Diet in Renal Disease (MDRD) equation.

6. Clarify why you are proposing to use a calcitonin assay that has a lower limit of quantification of 2 ng/L instead of the more sensitive calcitonin assay that you used in your New Drug Application.
7. We agree with the calculations of the number of patients needed in the study, subject to clinical input on the appropriateness of the assumption of a 1.8% event rate per year in this clinical population. Our understanding is that the study is designed to accumulate a total of approximately 611 adjudicated primary outcome events across the two study arms.
8. We note that the September 24, 2009 version of your protocol does not include an interim assessment of futility or superiority of the primary cardiovascular endpoint. In the event that liraglutide is approved during this review cycle, we will revisit the need for an interim analysis of futility in this study as part of the postmarketing requirements for liraglutide.
9. The statistical methods for the analysis of primary and supportive outcome data that are generally described in this protocol are acceptable. In addition, we request that you submit the more detailed statistical analysis plan with sufficient lead time prior to your analysis of data so that we may review the plan and send you our review comments.
10. This trial presents an opportunity to gain further information concerning the comparison between liraglutide and placebo in longitudinal changes in serum calcitonin in this study population. We recommend that the study protocol include a detailed analysis plan for evaluating this relationship. This analysis plan should include a pre-specified statistical analysis model, along with additional supportive analyses and descriptive summaries.
11. The Division is in the process of standardizing recommendations and definitions for cardiovascular endpoints for use by all sponsors who are developing treatments for type 2 diabetes. See the attached enclosures for the most recent version of these documents. Please note that these documents are still in draft form. Any additional modifications will be communicated to you.

If you have any questions, call John Bishai Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

- 1) Endpoints and Standardized Data Collection for Cardiovascular Outcomes Trials: Draft Recommendations
- 2) Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations



# Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations

Division of Metabolism and Endocrinology Products

Center for Office of Drug Evaluation and Research (CDER)

July 22, 2009  
Clinical/Medical

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## **Introduction**

The purpose of this document is to provide a framework of definitions for cardiovascular endpoint events in clinical trials. These definitions are based on clinical and research expertise, published guidelines and definitions, and our current understanding of cardiac biomarkers.

It is recognized that definitions of cardiovascular endpoints may change over time, as new biomarkers become available and enhance prior definitions or as standards evolve and thresholds of importance become modified. Nevertheless, endpoint definitions are necessary in clinical trials so that events are clearly characterized by objective criteria and reported uniformly. Advances in database technologies and statistical methodologies have created opportunities to aggregate large trial datasets. If uniformly defined, events in drug development programs or among different clinical trials may be analyzed more easily and trends and other safety signals may be identified.

All definitions have limitations, and there are challenges. The goal of this document is to propose definitions that will be accepted by the clinical community as important events that impact patient outcomes, by the regulatory agency as events that would be important to analyze for new drugs seeking approval or labeling changes, and by the research community where event rates and sample size calculations are critical to trial design and financial considerations.

Keeping in mind the value and limitations of any type of standardization, we propose the following definitions to simplify the conduct of cardiovascular outcomes trials.

## **CEC Operations**

In many cases, data are collected on subjects in clinical trials at a level where definitions can be applied objectively. However, if there are limited or missing data, the Clinical Endpoints Committee (CEC) for the clinical trial should adjudicate events based on their clinical expertise and the totality of the evidence.

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. CEC physicians will review all available information and use their clinical expertise to adjudicate the cause of death. Nevertheless, all deaths not attributed to the categories of cardiovascular death indicated in this document and not attributed to a non-cardiovascular cause will be presumed cardiovascular deaths.

Study sites should provide death certificates for all patients who have died. However, if a death certificate is the only information available for review, the CEC may decide not to use this information as a cause of death if another etiology appears to be more plausible.

100% source documentation of cardiac biomarker results should be performed in these clinical trials.

## **Evaluation of the Primary Endpoint**

**In cardiovascular trials, myocardial infarction is frequently the primary endpoint or a component of the primary endpoint.**

**Troponin is a continuous variable. However, adjudication in clinical trials requires dichotomous decisions.**

**Troponin assays have different reference limits for myocardial necrosis and myocardial infarction. Ultrasensitive troponin assays are expected to have even lower reference limits for myocardial necrosis and myocardial infarction. The prognostic significance of these reference limits needs to be determined and may affect a Division's perception of the safety in development programs.**

**Therefore, with respect to troponins, if the primary endpoint includes myocardial infarction, FDA requests two analyses:**

- 1. primary analysis in which the upper reference limit is the lowest value which satisfies a particular assay's criteria for myocardial necrosis**
- 2. primary analysis in which the upper reference limit is the lowest value which satisfies a particular assay's criteria for definite myocardial infarction**

**Both central and core laboratory results for cardiac biomarkers are acceptable.**

**Furthermore, the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, and the Agency recommends that sponsors evaluate outcomes separately for these two subsets of patients.**

## **APPENDIX 1. Definition of Cardiovascular Death**

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. Sudden Cardiac Death: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:
  - a. Witnessed and instantaneous without new or worsening symptoms
  - b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
  - c. Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)
  - d. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology
  - e. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided)
2. Death due to Acute Myocardial Infarction: death occurring up to 14 days after a documented acute myocardial infarction [verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus] and where there is no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

3. Death due to Heart Failure or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:
- a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
  - b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
  - c. Confinement to bed predominantly due to heart failure symptoms
  - d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
  - e. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m<sup>2</sup>

Cardiogenic shock can also be defined as SBP  $\geq$  90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint.

This category will include sudden death occurring during an admission for worsening heart failure.

4. **Death due to Cerebrovascular Event (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.**

**FDA Stroke Team Definition of Death due to Stroke: refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.**

5. **Death due to Other Cardiovascular Causes: death must be due to a fully documented cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, or cardiovascular intervention).**

## **APPENDIX 2. Definition of Non-Cardiovascular Death**

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorized as follows:

- **Pulmonary causes**
- **Renal causes**
- **Gastrointestinal causes**
- **Infection (includes sepsis)**
- **Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))**
- **Malignancy (i.e., new malignancy, worsening of prior malignancy)**
- **Hemorrhage, not intracranial**
- **Accidental/Trauma**
- **Suicide**
- **Non-cardiovascular system organ failure (e.g., hepatic failure)**
- **Non-cardiovascular surgery**
- **Other non-cardiovascular, specify: \_\_\_\_\_**



### **APPENDIX 3. Definition of Presumed Cardiovascular Death**

**Presumed Cardiovascular Death: All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint.**

## APPENDIX 4. Definition of Myocardial Infarction

### 1. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction.

- Spontaneous MI  
Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]\*
  - Development of pathological Q waves in the ECG\*\*
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

\*ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

- ST elevation  
New ST elevation at the J-point in two contiguous leads with the cut-off points:  
 $\geq 0.2$  mV in men or  $\geq 0.15$  mV in women in leads V2-V3 and/or  $\geq 0.1$  mV in other leads
- ST depression and T-wave changes  
New horizontal or down-sloping ST depression  $\geq 0.05$  mV in two contiguous leads; and/or T inversion  $\geq 0.1$  mV in two contiguous leads with prominent R-wave or R/S ratio  $> 1$ .

\*\*Pathological Q waves:

- Any Q-wave in leads V2-V3  $\geq 0.02$  seconds or QS complex in leads V2 and V3

Q-wave  $\geq 0.03$  seconds and  $\geq 0.1$  mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)

- Sudden, Unexpected Cardiac Death  
Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- Percutaneous Coronary Intervention-Related Myocardial Infarction  
For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99<sup>th</sup> percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99<sup>th</sup> percentile URL (Troponin or CK-MB > 3 x 99<sup>th</sup> percentile URL) are consistent with PCI-related myocardial infarction.

If the cardiac biomarker is elevated prior to PCI, a  $\geq 20\%$  increase of the value in the second cardiac biomarker sample within 24 hours of the PCI and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

Symptoms of cardiac ischemia are not required.

- Coronary Artery Bypass Grafting-Related Myocardial Infarction  
For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99<sup>th</sup> percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99<sup>th</sup> percentile URL (Troponin or CK-MB > 5 x 99<sup>th</sup> percentile URL) plus
  - either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram that persist through 30 days or new LBBB *or*
  - angiographically documented new graft or native coronary artery occlusion *or*
  - imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction.

If the cardiac biomarker is elevated prior to CABG, a  $\geq 20\%$  increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

- Pathological findings of an acute myocardial infarction
2. Criteria for Prior Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3  $\geq 0.02$  seconds or QS complex in leads V2 and V3

- Q-wave  $\geq 0.03$  seconds and  $\geq 0.1$  mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)<sup>a</sup>
- R-wave  $\geq 0.04$  seconds in V1-V2 and R/S  $\geq 1$  with a concordant positive T-wave in the absence of a conduction defect

<sup>a</sup>The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

### 3. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of the employed cardiac biomarker (troponin or CK-MB) is recommended. A second sample should be obtained 3-6 hours later. Recurrent infarction is diagnosed if there is a  $\geq 20\%$  increase of the value in the second sample. This value should also exceed the 99<sup>th</sup> percentile URL. However, if cardiac biomarkers are elevated prior to the suspected new MI, there must also be documentation of decreasing values (two samples at least 6 hours apart) prior to the suspected new MI. If the values for cardiac biomarkers are falling, criteria for reinfarction by further measurement of biomarkers together with the features of the ECG or imaging can be applied.

The ECG diagnosis of reinfarction following the initial infarction may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when ST elevation  $\geq 0.1$  mV reoccurs in an inpatient having a lesser degree of ST elevation or new pathognomonic Q waves, in at least two contiguous leads, particularly when associated with ischemic symptoms for 10 minutes or longer. The re-elevation of the ST segment can, however, also be seen in threatening myocardial rupture and should lead to additional diagnostic work-up. ST depression or LBBB on their own should not be considered valid criteria for myocardial infarction.

If biomarkers are increasing or peak is not reached, then there is insufficient data to diagnose recurrent MI.

#### 4. Clinical Classification of Different Types of Myocardial Infarction

For each myocardial infarction (MI) identified by the CEC, a Type of MI will be assigned using the following guidelines:

- **Type 1**  
**Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection**
- **Type 2**  
**Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension**
- **Type 3**  
**Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood**
- **Type 4a**  
**Myocardial infarction associated with PCI**
- **Type 4b**  
**Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy**
- **Type 5**  
**Myocardial infarction associated with CABG**

## APPENDIX 5. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as

1. No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis)

AND

2. Clinical Presentation (one of the following) with cardiac symptoms lasting  $\geq 10$  minutes and considered to be myocardial ischemia on final diagnosis

- Rest angina *or*
- New-onset (< 2 months) severe angina (Canadian Cardiovascular Society Grading Scale\* (or CCS classification system) classification severity  $\geq$  III) *or*
- Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS class III

AND

3. Requiring an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units)

AND

4. At least one of the following:

- a. New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:

- ST elevation  
New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points:
  - o  $\geq 0.2$  mV in men or  $\geq 0.15$  mV in women in leads V2-V3 and/or  $\geq 0.1$  mV in other leads
- ST depression and T-wave changes  
New horizontal or down-sloping ST depression  $\geq 0.05$  mV in two contiguous leads; and/or T inversion  $\geq 0.1$  mV in two contiguous leads with prominent R-wave or R/S ratio > 1.

- b. Evidence of ischemia on stress testing with cardiac imaging
- c. Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of  $\geq 70\%$  lesion and/or thrombus in an epicardial coronary artery *or* initiation/increased dosing of antianginal therapy.
- d. Angiographic evidence of  $\geq 70\%$  lesion and/or thrombus in an epicardial coronary artery

\*Grading of Angina Pectoris According to Canadian Cardiovascular Society Classification:

Class	Description of Stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

## APPENDIX 6. FDA Stroke Team Definition of Stroke

Stroke is an acute episode of neurological dysfunction attributed to a vascular cause.

### 1. Classification:

#### A. Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

#### B. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

#### C. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral, spinal, or retinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

#### D. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A, B, or C.

### 2. Stroke Disability

Stroke disability should be classified using the modified Rankin Scale ([www.strokecenter.org/trials/scales/rankin.html](http://www.strokecenter.org/trials/scales/rankin.html)) as follows:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead



## **APPENDIX 7. Definition of Stroke**

### **1. Transient Ischemic Attack**

**Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.**

### **2. Cerebrovascular Event (Stroke)**

**Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.**

**A. For the diagnosis of stroke, the following 4 criteria should be fulfilled:**

#### **1. Rapid onset\* of a focal/global neurological deficit with at least one of the following:**

- Change in level of consciousness**
- Hemiplegia**
- Hemiparesis**
- Numbness or sensory loss affecting one side of the body**
- Dysphasia/Aphasia**
- Hemianopia (loss of half of the field of vision of one or both eyes)**
- Amaurosis fugax (transient complete/partial loss of vision of one eye)**
- Other new neurological sign(s)/symptom(s) consistent with stroke**

**\*If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation**

**2. Duration of a focal/global neurological deficit  $\geq$  24 hours**

**OR**

**< 24 hours if**

- i. this is because of at least one of the following therapeutic interventions:**
  - a. Pharmacologic (i.e., thrombolytic drug administration)**
  - b. Non-pharmacologic (i.e., neurointerventional procedure (e.g. intracranial angioplasty))**

**or**

- ii. Available brain imaging clearly documents a new hemorrhage or infarct**

**or**

- iii. The neurological deficit results in death**

**3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)**

**4. Confirmation of the diagnosis by at least one of the following:\***

- a. Neurology or neurosurgical specialist**
- b. Brain imaging procedure (at least one of the following):**
  - i. CT scan**
  - ii. MRI scan**
  - iii. Cerebral vessel angiography**
- c. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)**

**\*if a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus will be mandatory.**

**B. If the acute focal signs represent a worsening of a previous deficit, these signs must have either**

- 1. Persisted for more than one week, or**
- 2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding**

C. Strokes are sub-classified as follows:

1. **Ischemic (Non-hemorrhagic):** a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology.
2. **Hemorrhagic:** a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,\* and primary subarachnoid hemorrhage.

\*All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.

3. **Unknown:** the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

D. Stroke Severity

Stroke severity can be classified using an adaptation of the modified Rankin Scale ([www.strokecenter.org/trials/scales/rankin.html](http://www.strokecenter.org/trials/scales/rankin.html)) as follows:

- a. **Mild:** no significant disability despite symptoms; able to carry out all usual duties and activities; or slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
- b. **Moderate:** moderate disability requiring some help but able to walk without assistance; or moderately severe disability such as unable to walk without assistance and unable to attend to own bodily needs without assistance.
- c. **Severe disability:** bedridden, incontinent, and requiring constant nursing care and attention; or death.

## **APPENDIX 8. Definition of Coronary Revascularization Procedures**

A coronary revascularization procedure is defined as either coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) (e.g., angioplasty, coronary stenting). CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as successful balloon inflation with or without stenting and the achievement of a residual stenosis < 50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy).

## **APPENDIX 9. Definition of Peripheral Revascularization Procedures**

A peripheral revascularization procedure is defined as vascular surgery or percutaneous intervention. Vascular surgery is defined as placement of a conduit with or without proximal and/or distal anastomoses. Percutaneous intervention is defined as successful balloon inflation with or without stenting and the achievement of a residual stenosis < 50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy)

Carotid revascularization will be differentiated from other peripheral vascular surgery or percutaneous interventions, such as abdominal aortic aneurysm repair, femoral popliteal bypass surgery, or other percutaneous peripheral intervention.

## **APPENDIX 10. Definition of Heart Failure Requiring Hospitalization**

Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

- a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available).

**AND**

- b. Clinical manifestations of heart failure including at least one of the following:

New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- edema
- pulmonary basilar crackles
- jugular venous distension
- new or worsening third heart sound or gallop rhythm, or
- radiological evidence of worsening heart failure.

**AND**

- c. Additional/Increased therapy

1. Initiation of intravenous diuretic, inotrope, or vasodilator therapy
2. Uptitration of intravenous therapy, if already on therapy
3. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

Biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

## APPENDIX 11. Definition of Stent Thrombosis (See Cutlip et al. and ARC Criteria)

### 1. Stent Thrombosis: Timing

Type	Timing
Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis	> 24 hours to 30 days after stent implantation
Late stent thrombosis†	> 30 days to 1 year after stent implantation
Very late stent thrombosis†	> 1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory.

\*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

### 2. ARC Definitions of Definite,\* Probable, and Possible Stent Thrombosis<sup>1</sup>

- Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathological confirmation:

- a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99<sup>th</sup> percentile of URL)
- Nonocclusive thrombus
  - Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream

- Occlusive thrombus

- TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

- b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

- Probable Stent Thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

July 22, 2009

- a. Any unexplained death within the first 30 days§
- b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- Possible Stent Thrombosis

**Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.**

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

## References

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2. Campeau L, Grading of angina pectoris (letter), *Circulation*, 1976, 54:522-23.
3. Cutlip DE, S Windecker, R Mehran, A Boam, DJ Cohen, G-A van Es, PG Steg, M-A Morel, L Mauri, P Vranckx, E McFadden, A Lansky, M Hamon, MW Krucoff, PW Serruys and on behalf of the Academic Research Consortium, Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions, *Circulation*, 2007, 115:2344-2351.
4. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; Definition and Evaluation of Transient Ischemic Attack, A Scientific Statement for Healthcare Professionals from the American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease, *Stroke*, 2009 Jun; 40(6):2276-93. Epub 2009 May 7. Review.
5. Thygesen, Kristian, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction, *Circulation*, 2007, 116:1-20.



Endpoints and Standardized Data  
Collection for Cardiovascular Outcomes  
Trials:  
Draft Recommendations

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research (CDER)

July 22, 2009  
Clinical/Medical

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## **APPENDIX 1. Primary Endpoint: General Recommendations for DMEP Cardiovascular Outcomes Trials**

Major Adverse Cardiovascular Events (MACE)

- 1. Cardiovascular Death (CV Death)**
- 2. Nonfatal Myocardial Infarction (NFMI)**
- 3. Nonfatal Stroke**

## APPENDIX 2. Enrichment of the Study Population

Enrollment of study subjects with higher risk characteristics, including:

- Duration of diabetes mellitus for at least 7 but preferably 10 years
- Insulin requiring diabetes mellitus
- Age  $\geq$  65 years of age
- History of acute coronary syndrome > 2 months from index event
- History of prior myocardial infarction
- History of prior coronary artery bypass graft (CABG) surgery
- History of prior percutaneous coronary intervention (PCI)
- History of hypertension
- History of hyperlipidemia
- History of coronary artery disease
- Family history of premature coronary artery disease
- History of tobacco use
  - any use (# of years)
    - current use
    - prior use
  - never used
- Peripheral vascular disease
- History of carotid/vertebral artery disease
- History of transient ischemic attack (TIA) or stroke
- History of congestive heart failure
- Renal insufficiency
  - glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup> per MDRD or  $< 60$  mL/min per Cockcroft-Gault equation
  - Urine Albumin to Urine Creatinine Ratio
    - microalbuminuria (30-300 mg Albumin/g Creatinine)
    - macroalbuminuria ( $> 300$  mg Albumin/g Creatinine)
- History of arrhythmia

### APPENDIX 3. Endpoints of Interest that Require Adjudication

- **Death**
  - All Cause Mortality
  - Cardiovascular Death
  - Non-Cardiovascular Death
- **Acute Coronary Syndrome**
  - Myocardial Infarction
  - Hospitalization for Unstable Angina
- **Cerebrovascular Events**
  - Cerebrovascular Event (Stroke)
    - Ischemic (Non-hemorrhagic)
    - Hemorrhagic
    - Unknown
  - Transient Ischemic Attack
- **Coronary Revascularization Procedures**
  - Coronary Artery Bypass Graft Surgery
  - Percutaneous Coronary Intervention
- **Hospitalization for Heart Failure**
- **Stent Thrombosis (clinical adjudication)**
  - Data needed
    - Name of device (Bare metal stent versus Drug eluting stent) as well as stent diameter and length
    - Coronary reference vessel diameter (RVD) and lesion length
    - Date of implantation
    - Date of stent thrombosis
    - Indication for index PCI [ACS (indicate STEMI, non-STEMI, or UAP), non-ACS]
    - Did patient have multivessel disease?
    - Did patient undergo multivessel (three-vessel disease) or left main treatment?
    - Left ventricular function
    - Overlapping stents
    - Bifurcation lesion stenting
    - Bypass graft (arterial or venous conduit) stenting
    - Presence or absence of renal disease based on glomerular filtration rate as determined by the Cockcroft-Gault Equation
    - Was patient on dual antiplatelet therapy (yes/no), and if not, date of aspirin or P2Y12 inhibitor discontinuation?

#### **APPENDIX 4. Other Endpoints of Interest that Do Not Require Formal Adjudication**

- **Hospitalization for other CV causes**
  - **Pulmonary Embolus**
  - **Aortic Dissection**
  - **Ruptured Aortic Aneurysm**
- **Carotid Artery Revascularization (surgical versus percutaneous)**
- **Other Peripheral Vascular Revascularization (lower extremity, renal, mesenteric, iliac, subclavian, and aortic etc.) (surgical versus percutaneous)**
- **Lower Extremity Amputation**
- **Hospitalization for Cardiac Arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement)**

## **APPENDIX 5. Source Documents**

Check boxes should be created so that investigator reported adverse events will trigger Clinical Endpoints Committee (CEC) review. Check boxes should also be created for CEC adjudication. Records should be obtained for all hospitalizations, and autopsies should be obtained for all deaths and submitted to the CEC for review. Source documents are needed for events to include but not be limited to:

1. **Death**
  - a. Autopsy (if performed)
  - b. Code summary (if available)
  - c. Death/Hospital summary (if death occurred in-hospital)
  
2. **Myocardial Infarction/Hospitalization for Unstable Angina/Stent Thrombosis**
  - a. Admission History and Physical
  - b. ECG tracings (prior to event, during event, and following event resolution)
  - c. Cardiac biomarkers (all troponin/CK-MB results for hospitalization and prior 30 days) Record units, normal ranges, and myocardial necrosis and myocardial infarction reference limits)
  - d. Other laboratory reports, if requested
  - e. Procedure reports (Cardiac Catheterization, PCI, CABG)
  - f. Other imaging reports (MRI, CTA, Echocardiogram, Nuclear Medicine)
  - g. Discharge Summary
  
3. **Stroke or TIA**
  - a. Neurology Consult
  - b. Imaging reports (MRI, CT, or other imaging reports including transthoracic and/or transesophageal echocardiograms)
  - c. Discharge Summary
  
4. **Coronary Revascularization Procedures**
  - a. Procedure reports (Cardiac catheterization, PCI, CABG)
  - b. Discharge Summary
  
5. **Hospitalization for Heart Failure**
  - a. Admission History and Physical
  - b. ECG tracings
  - c. Cardiac markers (troponin/CK-MB results)
  - d. Other laboratory reports (e.g., BNP)
  - e. Chest X-Ray report
  - f. Discharge Summary
  
6. **Acute Pancreatitis**
  - a. Imaging reports
  - b. Discharge Summary

## **APPENDIX 6. Information to be Submitted for the Cardiovascular Outcomes Trial**

The sponsor should submit the following information for Division review prior to initiating their Cardiovascular Outcomes Trial:

- **Proposed protocol**
- **Definitions for all protocol endpoints and events of special interest**
- **Case Report Form**
- **Clinical Endpoints Committee (CEC) Charter, including algorithms to be used for endpoint events**
- **Statistical Analysis Plan (SAP)**



## **APPENDIX 7. Data Sets to be Submitted with the Clinical Study Report**

**The Division requires that verbatim terms are included in the adverse events data sets submitted to the Agency.**

NOTE: All raw data sets as well as derived data sets are to be submitted with the Clinical Study Report.

## **APPENDIX 8. Listings to be Submitted with the Clinical Study Report**

All of the prospectively collected cardiovascular (CV) events described in Appendix 3 should be reviewed by the Clinical Events Committee (CEC), as discrepancies between investigator-reported and adjudicated events may arise. With the clinical study report, the sponsor should submit data sets for both the investigator-reported and CEC adjudicated cardiovascular events. Additionally, the sponsor should submit the following 5 listings:

- All investigator-reported CV events
- All CEC-adjudicated CV events
- All investigator-reported CV events that were also adjudicated by the CEC to be events
- All investigator-reported CV events that were not thought to be events by the CEC (“downgrades”)
- All CEC-adjudicated CV events that were not considered to be events by the investigator (“upgrades”)

## **APPENDIX 9. Standardised MedDRA Queries (SMQs) for DMEP Cardiovascular Outcomes Trials**

In addition to CEC adjudication of triggered events, we recommend searching the following standardised MedDRA queries (SMQs) for other possible cardiovascular events that may also require adjudication:

1. Myocardial Infarction
2. Ischaemic Heart Disease
3. Cardiac Arrhythmias
4. Cardiac Failure
5. Embolic and Thrombotic Events
6. Shock
7. Torsade de pointes/QT prolongation
8. Cerebrovascular Disorders
9. Central Nervous System Haemorrhages and Cerebrovascular Accidents
10. Vasculitis

## **APPENDIX 10. System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Cardiovascular Outcomes Trials**

The Division also recommends searching the following system organ classes (SOCs), high level terms (HLT), lower level terms (LLTs), and preferred terms (PTs) for cardiovascular events that may also require adjudication:

1. SOC: Cardiac Disorders
2. SOC: General Disorders and Administration Site Conditions
3. SOC: Injury, Poisoning, and Procedural Complications
4. SOC: Investigations
5. SOC: Musculoskeletal and Connective Tissue Disorders
6. SOC: Nervous System Disorders
7. SOC: Respiratory, Thoracic, and Mediastinal Disorders
8. SOC: Surgical and Medical Procedures
9. SOC: Vascular Disorders
10. LLT: Cerebral Revascularization Synangiosis (search value: revascularization)
11. LLT: Coronary Revascularization (search value: revascularization)
12. LLT: Peripheral Revascularization (search value: revascularization)
13. LLT: Renal Revascularization (search value: revascularization)
14. LLT: Transmyocardial Revascularization (search value: revascularization)
15. LLT: Acute myocardial ischemia (search value: myocardial ischemia)
16. LLT: ECG signs of myocardial ischemia (search value: myocardial ischemia)
17. LLT: Myocardial ischemia (search value: myocardial ischemia)
18. LLT: Myocardial ischemia recurrent (search value: myocardial ischemia)
19. LLT: Silent myocardial ischemia (search value: myocardial ischemia)
20. PT: Acute Myocardial Infarction (search value: myocardial infarction)
21. PT: Myocardial Infarction (search value: myocardial infarction)
22. PT: Post Procedural Myocardial Infarction (search value: myocardial infarction)
23. PT: Silent Myocardial Infarction (search value: myocardial infarction)

## **APPENDIX 11. Standardised MedDRA Queries (SMQs), System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Obesity Trials**

In addition to CEC adjudication of triggered events, we recommend searching the following standardised MedDRA queries (SMQs) for other possible cardiovascular events that may also require adjudication:

### Standardised MedDRA Queries (SMQs)

1. Myocardial Infarction
2. Ischaemic Heart Disease
3. Cardiac Arrhythmias
4. Cardiac Failure
5. Cardiomyopathy
6. Embolic and Thrombotic Events
7. Hypertension
8. Pulmonary Hypertension
9. Rhabdomyolysis/Myopathy
10. Shock
11. Torsade de pointes/QT prolongation
12. Cerebrovascular Disorders
13. Central Nervous System Haemorrhages and Cerebrovascular Accidents
14. Vasculitis

Furthermore, the Division also recommends searching the following system organ classes (SOCs), high level terms (HLT), lower level terms (LLTs), and preferred terms (PTs) for cardiovascular events that may also require adjudication:

1. SOC: Cardiac Disorders
2. SOC: General Disorders and Administration Site Conditions
3. SOC: Injury, Poisoning, and Procedural Complications
4. SOC: Investigations
5. SOC: Musculoskeletal and Connective Tissue Disorders
6. SOC: Nervous System Disorders
7. SOC: Respiratory, Thoracic, and Mediastinal Disorders
8. SOC: Surgical and Medical Procedures
9. SOC: Vascular Disorders
10. HLT: Cardiac valve disorders NEC
11. HLT: Pulmonary hypertensions
12. LLT: Cardiac valvulopathy
13. LLT: Cerebral Revascularization Synangiosis (search value: revascularization)
14. LLT: Coronary Revascularization (search value: revascularization)
15. LLT: Peripheral Revascularization (search value: revascularization)
16. LLT: Renal Revascularization (search value: revascularization)
17. LLT: Transmyocardial Revascularization (search value: revascularization)
18. LLT: Acute myocardial ischemia (search value: myocardial ischemia)
19. LLT: ECG signs of myocardial ischemia (search value: myocardial ischemia)
20. LLT: Myocardial ischemia (search value: myocardial ischemia)
21. LLT: Myocardial ischemia recurrent (search value: myocardial ischemia)
22. LLT: Silent myocardial ischemia (search value: myocardial ischemia)
23. PT: Acute Myocardial Infarction (search value: myocardial infarction)
24. PT: Myocardial Infarction (search value: myocardial infarction)
25. PT: Post Procedural Myocardial Infarction (search value: myocardial infarction)
26. PT: Silent Myocardial Infarction (search value: myocardial infarction)
27. PT: Cardiac valve disease
28. PT: Pulmonary hypertension

## **APPENDIX 12. Recommended Methods of Addressing Elevated CPKs at Routine Follow-Up Appointments in DMEP Clinical Trials**

**For creatine phosphokinase elevation of > 2X ULN, the investigator should clearly document (by use of a check-box) whether or not symptoms consistent with a cardiac etiology coincided with this elevation. If coincident cardiac symptoms were reported, additional testing with 12-lead electrocardiograms and troponins should be considered.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ADA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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

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/s/

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MARY H PARKS  
10/07/2009

**NDA Amendment - Labeling**



October 5, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza (liraglutide [rDNA origin] injection)  
NDA Amendment: Response to FDA Comments on September 28<sup>th</sup> Draft  
Physician Insert**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza (liraglutide [rDNA origin] injection) submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments on the draft Physician Insert received in an e-mail from FDA Project Manager, John Bishai on September 28, 2009.

All FDA's recommendations have been reviewed, and, in response, we are returning the draft Physician Insert with tracked changes to indicate Novo Nordisk's acceptances of FDA requests, as well as proposed revisions.

Novo Nordisk has also noted areas in the proposed Physician Insert where we would appreciate the opportunity to discuss further with the Division in a teleconference as we believe that this approach will allow more efficient resolution of outstanding questions.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5757 created on September 30, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
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Sincerely,  
NOVO NORDISK INC.

Lois Kotoskie on  
behalf of Mary  
Ann McElligott

Digitally signed by Lois Kotoskie on  
behalf of Mary Ann McElligott  
DN: cn=Lois Kotoskie on behalf of Mary  
Ann McElligott, o=Novo Nordisk Inc.,  
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Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
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**NDA Amendment - Labeling**



September 30, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341**

**Victoza (liraglutide [rDNA origin] injection)**

**NDA Amendment: Revised Labeling (Carton, Container, and Instructions for Use)**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 28, 2009 e-mail from John Bishai, Regulatory Project Manager, in which revised labeling for carton, container, and Instructions for Use was requested.

At this time we are providing the revised labeling as an amendment to NDA 22-341.

This submission is being provided electronically (approximately 5 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5754 created on September 27, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo Nordisk  
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mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

**NDA Amendment**



September 29, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Responses to FDA request for information dated  
September 18, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 18, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5754 created on September 27, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on behalf  
of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.09.29 14:45:59 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and herby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
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**NDA Amendment**



September 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA request for information dated September 22,  
2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 22, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5750 created on September 23, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
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Princeton, NJ 08540  
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Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.09.25 15:35:45 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
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**NDA Amendment**



September 23, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® (liraglutide [rDNA origin] injection)  
NDA Amendment – Response to FDA request for information dated September 15,  
2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the September 15, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5747 created on September 20, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
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Sincerely,

NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on behalf  
of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
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Date: 2009.09.23 15:54:41 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
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**NDA Amendment**



September 22, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Responses to FDA requests for information dated  
September 9 and 14, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 9 and 14, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5747 created on September 20, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary Ann  
McElligott

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
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Associate Vice President, Regulatory Affairs  
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Sent via FDA Gateway

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Princeton, NJ 08540  
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**NDA Amendment**



September 17, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated  
September 17, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 17, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5740 created on September 13, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary  
Ann McElligott**

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.09.17 14:37:53 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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**NDA Amendment**



September 16, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated  
September 9, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the September 9, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information on thyroidectomies as an Amendment to NDA 22-341. We will follow-up in a separate amendment with the response to the remaining request from this date.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5740 created on September 13, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary Ann  
McElligott

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.09.16 14:27:25 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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mamc@novonordisk.com

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
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www.novonordisk-us.com

**NDA Amendment**



September 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA Requests for Information dated August 27 and**  
**September 2, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the August 27 and September 2, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5736 created on September 9, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.



Sincerely,  
NOVO NORDISK INC.

Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.09.11 14:01:10 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
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mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

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Princeton, NJ 08540  
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www.novonordisk-us.com

**NDA Amendment - Labeling**



September 4, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA Comments on August 28<sup>th</sup> Draft Physician Insert**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to FDA comments on the draft Physician Insert received in an e-mail from FDA Project Manager, John Bishai on August 28, 2009.

All FDA's recommendations have been reviewed, and, in response, we are returning the draft Physician Insert with tracked changes to indicate Novo Nordisk's acceptances of FDA requests, as well as proposed revisions.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5729 created on September 3, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Robert Fischer

on behalf of Mary

Ann McElligott

Digitally signed by Robert Fischer on behalf of  
Mary Ann McElligott  
DN: cn=Robert Fischer on behalf of Mary Ann  
McElligott, o=US, ou=Novo Nordisk Inc.,  
ou=Regulatory Affairs,  
email=rof@novonordisk.com  
Reason: I am approving this document  
Date: 2009.09.04 09:34:19 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
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**NDA Amendment**



September 4, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Amundson Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Responses to FDA requests for information dated**  
**August 26 and 31, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the August 26 and 31, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5729 created on September 3, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,

NOVO NORDISK INC.

**Lewis R. Pollack**

on behalf of Mary

**Ann McElligott**

Digitally signed by Lewis R. Pollack on  
behalf of Mary Ann McElligott  
DN: cn=Lewis R. Pollack on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs,  
email=lewpp@novonordisk.com  
Date: 2009.09.04 13:39:17 -04'00'

Mary Ann McElligott, Ph.D.

Associate Vice President, Regulatory Affairs

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Sent via FDA Gateway

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**Novo Nordisk Inc.**

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**NDA Amendment**



September 2, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Responses to FDA request for information dated August 20 and  
26, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the August 20 and 26, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5725 created on August 30, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Lois Kotkoskie on behalf  
of Mary Ann McElligott

Digitally signed by Lois Kotkoskie on behalf of Mary Ann  
McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US,  
o=Novo Nordisk Inc, ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.09.02 15:20:26 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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609-987-5831 (direct)  
mamc@novonordisk.com

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MEMORANDUM

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

---

DATE: August 31, 2009

FROM: Xikui Chen, Ph.D.  
Division of Scientific Investigations (DSI)

THROUGH: C.T. Viswanathan, Ph.D. *Michael Kelly for Martin Yon*  
Associate Director - Bioequivalence  
Division of Scientific Investigations

TO: Mary H. Parks, M.D.  
Director, Division of Metabolic and Endocrine Products  
(DMEP)

SUBJECT: Addendum to Review of EIR Covering NDA 22-341,  
Victoza® [Liraglutide Injection], Sponsored by Novo  
Nordisk A/S Global Development

This is an addendum to the DSI inspection summary memo dated February 18, 2009, concerning the analytical portion of the following bioequivalence (BE) study.

**Study** NN2211-1692: A randomized, double-blind, single-centre, two-period, cross-over trial in healthy subjects investigating the bioequivalence between the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4)

In this addendum, DSI evaluates NOVO NORDISK's response letter (March 27, 2009) to the Form FDA-483 issued to the analytical site, \_\_\_\_\_

b(4)

**Background Information**

In the analytical inspection summary memo (February 18, 2009) to DMEP, DSI recommended that \_\_\_\_\_ (the analytical study site) should re-calculate calibration curves for all analytical runs in a consistent manner using explicit and objective criteria for calibration standard and run acceptance. Only the subject concentrations from analytical runs that meet these QC acceptance criteria should be used for bioequivalence assessment, and bioequivalence should be reevaluated using the valid data only.

b(4)



**NOVO NORDISK's Response**

b(4)

In the response dated March 27, 2009, Novo Nordisk stated that the following run acceptance criteria were established after the DSI inspection at \_\_\_\_\_

**Acceptance criteria for calibration curve:** The mean of duplicate back-calculated calibrators >129 pmol/L shall be within  $\pm 20\%$  of the nominal values, except the mean of back-calculated calibrators below 129 pmol/L shall be within  $\pm 30\%$  of the nominal values. A maximum of 3 calibrator determinations may be rejected. No single calibrator determination can be rejected unless the mean of the duplicate determinations is outside  $\pm 30\%$  (<129 pmol/L) or  $\pm 20\%$  (>129 pmol/L), and the CV of the duplicate determinations is  $>30\%$ .

**Acceptance criteria for QC samples:** Maximally one QC sample from each concentration may have an inaccuracy greater than  $\pm 20\%$  from the target value, and no more than two of the six determinations (two low, two medium, and two high) may have an inaccuracy greater than  $\pm 20\%$  from the target values.

Based on the run acceptance criteria stated above, 20 of the 59 originally accepted runs were rejected for Study NN2211-1692. After eliminating these nonvalid data, the reduced dataset was recalculated for pharmacokinetics and statistical bioequivalence. Novo Nordisk claimed that the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4) remain bioequivalent with the reduced dataset only.

**DSI Evaluation and Conclusion:**

DSI reviewed the acceptance criteria for calibration curves and QC samples used by Novo Nordisk, and found them to be adequate. We recommend that data generated from the 39 acceptable analytical runs can be accepted for review. Tables of these data were included in the submission dated March 27, 2009, in the electronic document room.

Please note that this addendum evaluates only the response letter from Novo Nordisk concerning the analytical issues. DSI's evaluation of the Form FDA-483 response letter (February 8, 2009) from the clinical site ( \_\_\_\_\_ ) was forwarded to DMEP in a separate memo dated February 25, 2009.

b(4)



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/s/  
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XIKUI CHEN

09/01/2009

Hard copies available upon request

## REQUEST FOR CONSULTATION

TO (Division/Office):  
**CDER OSE Consults**  
**Mildred Wright**  
**Office of Safety and Epidemiology**  
**Email: [mildred.wright@fda.hhs.gov](mailto:mildred.wright@fda.hhs.gov)**  
**WO22 RM 4492, Phone: 796-1027**

FROM:  
**John Bishai, Ph.D.**  
**Regulatory Project Manager**  
**DMEP, HFD-510, Phone: 796-1311**

DATE August 28, 2009	IND NO.	NDA NO. 22,341	TYPE OF DOCUMENT REMS/Medguide	DATE OF DOCUMENT July 8, 2009
NAME OF DRUG Victoza (liraglutide injection)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Treatment of Type II Diabetes	DESIRED COMPLETION DATE September 15, 2009
NAME OF FIRM: Novo Nordisk				

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING            | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING    | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION               | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input checked="" type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA                  | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT         | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |   |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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#### COMMENTS/SPECIAL INSTRUCTIONS:

This is a consult request for a REMS Supporting Document for the Evaluation of Pancreatic Safety using a Prospective Claims Safety Surveillance Database Study (i3 Aperio). The documents are in the EDR, direct links are below:  
Cover Letter: <\\cdsesub1\evsprod\NDA022341\0039\m1\us\102-cover-letters\cover.pdf>  
REMS supporting document (PDF): <\\CDSESUB1\EVSPROD\NDA022341\0039\m1\us\116-risk-mgt\proposed-rems-support.pdf>

SIGNATURE OF REQUESTER John Bishai	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

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JOHN M BISHAI  
08/28/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>CDER OSE Consults</b> <b>Mildred Wright</b> <b>Office of Safety and Epidemiology</b> <b>Email: <a href="mailto:mildred.wright@fda.hhs.gov">mildred.wright@fda.hhs.gov</a></b> <b>WO22 RM 4492, Phone: 796-1027</b>		FROM: <b>John Bishai, Ph.D.</b> <b>Regulatory Project Manager</b> <b>DMEP, HFD-510, Phone: 796-1311</b>		
DATE August 28, 2009	IND NO.	NDA NO. 22,341	TYPE OF DOCUMENT REMS/Medguide	DATE OF DOCUMENT July 8, 2009
NAME OF DRUG Victoza (liraglutide injection)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Treatment of Type II Diabetes	DESIRED COMPLETION DATE September 15, 2009	
NAME OF FIRM: Novo Nordisk				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
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<p>This is a consult request for a REMS Supporting Document for the Evaluation of Knowledge, Attitude, and Behavior Surveys. The documents are in the EDR, direct links are below:          Cover Letter: <a href="#">\\cdsesub1\evsprod\NDA022341\0039\m1\us\102-cover-letters\cover.pdf</a>          REMS supporting document (PDF): <a href="#">\\CDSESUB1\EVSPROD\NDA022341\0039\m1\us\116-risk-mgt\proposed-rems-support.pdf</a></p>				
SIGNATURE OF REQUESTER John Bishai		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

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JOHN M BISHAI  
08/28/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>CDER OSE Consults Mildred Wright Office of Safety and Epidemiology Email: <a href="mailto:mildred.wright@fda.hhs.gov">mildred.wright@fda.hhs.gov</a> WO22 RM 4492, Phone: 796-1027</b>		FROM: <b>John Bishai, Ph.D. Regulatory Project Manager DMEP, HFD-510, Phone: 796-1311</b>		
DATE August 28, 2009	IND NO.	NDA NO. 22,341	TYPE OF DOCUMENT REMS/Medguide	DATE OF DOCUMENT July 8, 2009
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<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
<p>This is a consult request for a REMS Supporting Document for the Evaluation of Case Series Registry to Evaluate Medullary Thyroid Carcinoma. The documents are in the EDR, direct links are below:  Cover Letter: <a href="#">\\cdsesub1\evsprod\NDA022341\0039\m1\us\102-cover-letters\cover.pdf</a>  REMS supporting document (PDF): <a href="#">\\CDSESUB1\EVSPROD\NDA022341\0039\m1\us\116-risk-mgt\proposed-rems-support.pdf</a></p>				
SIGNATURE OF REQUESTER John Bishai		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/  
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JOHN M BISHAI  
08/28/2009

**NDA Amendment**



August 28, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated August 28, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the August 28, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5721 created on August 26, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson on behalf  
of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.08.28 15:03:41 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

**NDA Amendment**



August 28, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA requests for information dated August 26, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the August 26, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing responses to three of the requests as an Amendment to NDA 22-341.

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Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.08.28 14:52:18 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

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Princeton, NJ 08540  
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**NDA Amendment**



August 27, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA requests for information dated August 14, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the August 14, 2009 requests from FDA Project Manager, John Bishai.

One of the August 14<sup>th</sup> requests was for further clarification on programming errors and that response is provided in this amendment. The second request was for information on patients taking proton pump inhibitors; this information was provided in an amendment on August 25, 2009.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5718 created on August 23, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

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**Novo Nordisk Inc.**  
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Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of  
Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.08.27 12:02:19 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
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## NDA Amendment



August 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)



Sincerely,  
NOVO NORDISK INC.

Lois Kotkoskie on  
behalf of Mary Ann  
McElligott

Digitally signed by Lois Kotkoskie on behalf of Mary Ann  
McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=loko@novonordisk.com  
Date: 2009.08.25 12:32:39 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

**Aljuburi, Lina**

**From:** Aljuburi, Lina  
**Sent:** Thursday, August 20, 2009 9:54 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** Bishai, John  
**Subject:** Information requests regarding NDA 22-341 liraglutide injection

Good morning Michelle,

We have the following information requests regarding NDA 22-341 liraglutide injection.

1. Please complete the following table. For "active comparator", you can group all active comparators together - no need to have a separate column for each type of active comparator.

Table X. Patient exposures to liraglutide								
	Lira 0.6 mg	Lira >0.6 to <1.2 mg	Lira 1.2 mg	Lira >1.2 to <1.8 mg	Lira 1.8 mg	Lira >1.8 mg	Placebo	Active comparator
<b>At NDA filing</b>								
≥24 weeks								
≥50 weeks								
≥52 weeks								
≥76 weeks								
Patient-years (all trials)								
Patient-years (phase 3 trials)								
<b>At 120-day safety update</b>								
≥24 weeks								
≥50 weeks								
≥52 weeks								
≥76 weeks								
Patient-years (all trials)								
Patient-years (phase 3 trials)								

2. In Table 1-3, page 34, ISS, Module 5.3.5.3., you report that there were 840 patients with type 2 diabetes treated with liraglutide for ≥50 weeks. In the safety update (Table 1-5, page 21), you still report 840 patients with type 2 diabetes treated with liraglutide for ≥50 weeks. Please confirm whether these exposures are correct. Because there are more patient data from the extension trials included in the 120-day safety update, shouldn't some patients within 3 months of the 50-week timepoint at the time of NDA data cutoff have reached the 50-week timepoint at the time of data cutoff for the 120-day safety update?

Feel free to contact John or me if you have any questions.

Many thanks,  
Lina

**Lina AlJuburi, Pharm.D., M.S.**  
**Chief, Project Management Staff**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**[l.aljuburi@fda.hhs.gov](mailto:l.aljuburi@fda.hhs.gov)**  
**301-796-1168 (phone)**  
**301-796-9712 (fax)**

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

LINA ALJUBURI  
08/20/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 22-341  
IND 61,040

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Novo Nordisk Inc.  
100 College Road West  
Princeton, New Jersey 08540

Attention: Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Dear Dr. McElligott:

Please refer to your New Drug Application (NDA) dated May 23, 2008, received May 23, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liraglutide Injection, 6 mg/mL.

In your NDA you requested review of the proposed proprietary name, Victoza. We have completed our review of Victoza, and have concluded that it is acceptable.

The proposed proprietary name, Victoza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 23, 2008 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 Millie Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1027. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, John Bishai at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

-----  
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/s/  
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CAROL A HOLQUIST  
08/12/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-341  
IND 61,040

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Novo Nordisk Inc.  
100 College Road West  
Princeton, New Jersey 08540

8/12/09

Attention: Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Dear Dr. McElligott:

Please refer to your New Drug Application (NDA) dated May 23, 2008, received May 23, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liraglutide Injection, 6 mg/mL.

In your NDA you requested review of the proposed proprietary name, Victoza. We have completed our review of Victoza, and have concluded that it is acceptable.

The proposed proprietary name, Victoza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 23, 2008 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 Millie Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1027. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, John Bishai at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

---

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

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/s/

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CAROL A HOLQUIST  
08/12/2009



**NDA Amendment**



August 12, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated August 5, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the August 5, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5740 created on August 9, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
Lois Kotkoskie on  
behalf of Mary Ann  
McElligott

Digitally signed by Lois Kotkoskie on behalf of Mary  
Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=loko@novonordisk.  
com  
Date: 2009.08.12 11:39:53 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
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**NDA Amendment**



August 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA Comments Dated August 5, 2009**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the August 5, 2009 comments received from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the responses as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5699 created on August 5, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann  
McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=loko@novonordisk.com  
Date: 2009.08.11 10:21:34 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
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609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
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**NDA Amendment**



August 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Final Report from a Human Factor Study**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the July 20, 2009 contact with FDA Project Manager, John Bishai where he discussed the ongoing device review.

At this time, Novo Nordisk is providing the final report from a Human Factor Study conducted with the Victoza Pens to facilitate the ongoing device review.

This amendment is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5699 created on August 5, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,

NOVO NORDISK INC.

Lois Kotkoskie on  
behalf of Mary  
Ann McElligott

Digitally signed by Lois Kotkoskie on  
behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of  
Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.08.11 09:28:42 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mame@novonordisk.com

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
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**NDA Amendment**



August 6, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated July 14, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the July 14, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5696 created on August 2, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.

**Lewis R. Pollack on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lewis R. Pollack on behalf of  
Mary Ann McElligott  
DN: cn=Lewis R. Pollack on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs, email=lewp@novonordisk.  
com  
Date: 2009.08.06 14:06:38 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
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**NDA Amendment**



August 5, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated August 4, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the August 4, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information. Attached are case report forms (CRFs) for patients 579008, 128005, 129006 179001 and 212004.

This amendment is being provided electronically (approximately 10 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5696 created on August 2, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary  
Ann McElligott**

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behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk  
Inc, ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.08.05 15:29:35 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

NDA Amendment



July 29, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated July 23, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the July 23, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5689 created on July 26, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary  
Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=loko@novonordisk.com  
Date: 2009.07.29 12:24:26 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

**Bishai, John**

---

**From:** MTHO (Michelle Thompson) [mtho@novonordisk.com]  
**Sent:** Thursday, July 16, 2009 5:04 PM  
**To:** Bishai, John  
**Subject:** RE: NDA 22-341 (liraglutide): Additional language for inclusion in informed consent text  
**Attachments:** mmsinfo.txt; emfinfo.txt

Hi John,

We accept the Division's recommended language noted below. Please let me know if you have any additional questions.

Best regards,

Michelle

---

**From:** Bishai, John [mailto:John.Bishai@fda.hhs.gov]  
**Sent:** Thursday, July 16, 2009 10:42 AM  
**To:** MTHO (Michelle Thompson)  
**Subject:** RE: NDA 22-341 (liraglutide): Additional language for inclusion in informed consent text

Hello Michelle,

Below you will find our revisions to your proposed pediatric informed consent form, dated July 14th. Please confirm that Novo Nordisk accepts the changes recommended below.

For short-term trials (<6 months):

When liraglutide was given to rats and mice for most of their lifetime, it caused tumors, called "C-cell tumors", of the thyroid gland. Some of these tumors were cancers. It is not known whether liraglutide will cause C-cell tumors or cancer in people. Short periods of treatment with liraglutide are not expected to cause these tumors in people. In people, C-cell cancers (called "medullary thyroid carcinoma") often make extra amounts of a hormone called calcitonin, which can be detected with a blood test. Liraglutide has been tested in more than 3500 adults and about 600 adults have been given liraglutide for 2 years. In these studies, liraglutide did not cause big changes in blood calcitonin levels. In mice, liraglutide also caused cancers underneath the skin where liraglutide was injected. These cancers are called "fibrosarcomas". It is not known if liraglutide will cause fibrosarcomas in people. Short periods of treatment with liraglutide are not expected to cause these tumors in people.

For long-term trials (>=6 months):

When liraglutide was given to rats and mice for most of their lifetime, it caused tumors, called "C-cell tumors", of the thyroid gland. Some of these tumors were cancers. It is not known whether liraglutide will cause C-cell tumors or cancer in people. In people, C-cell cancers (called "medullary thyroid carcinoma") often make extra amounts of a hormone called calcitonin, which can be detected with a blood test. Liraglutide has been tested in more than 3500 people adults and about 600 adults have been given liraglutide for 2 years. In these studies, liraglutide did not cause big changes in blood calcitonin levels. During the study, you will have blood drawn at certain times to check your level of calcitonin. If your calcitonin is high, you may need other tests to look for medullary thyroid carcinoma. People suspected of having medullary thyroid carcinoma will have an operation to take out their thyroid gland. If medullary thyroid carcinoma has not spread outside the thyroid gland, they are usually cured. In mice, liraglutide also caused cancers underneath the skin where liraglutide was injected. These cancers are called "fibrosarcomas". It is not known if liraglutide will cause fibrosarcomas in people.

7/23/2009

Thanks,  
John

---

**From:** MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]  
**Sent:** Tuesday, July 14, 2009 1:37 PM  
**To:** Bishai, John  
**Subject:** NDA 22-341 (liraglutide): Additional language for inclusion in informed consent text

Hi John,

Here is our proposal for inclusion of NN language in the IC text:

For short-term trials (<6 months):

[Redacted]

[Redacted]

For long-term trials (>=6 months):

[Redacted]

[Redacted]

b(4)

Please let me know if you have any questions on the proposed. Thank you.

Michelle

---

**Michelle Thompson**  
Director, Regulatory Affairs  
Strategic Business Development

Novo Nordisk Inc.  
100 College Road West  
Princeton, New Jersey 08540  
USA  
(609)987-5972 (direct)  
(609)933-5079 (mobile)  
MTHO@novonordisk.com

7/23/2009

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/s/

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John M Bishai  
7/23/2009 01:59:34 PM  
CSO



## Bishai, John

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**From:** Bishai, John  
**Sent:** Tuesday, July 14, 2009 8:04 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** Info request for NDA 22-341

Hello Michelle,

I have a information request for serum creatinine. Specifically for the set of all completed Phase 2 and Phase 3 trials of liraglutide, please provide the number and percentage of patients who had normal baseline serum creatinine, and who developed serum creatinine values in the following ranges:

>ULN  
≥1.5x ULN  
≥2x ULN  
≥3x ULN  
≥5x ULN  
≥10x ULN

Please provide the data by liraglutide dose, and include pooled placebo and pooled active comparator groups.

If you have any questions, please feel free to contact me.

Thanks,  
John

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/s/

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John M Bishai  
7/23/2009 02:49:26 PM  
CSO

## Bishai, John

---

**From:** Bishai, John  
**Sent:** Wednesday, June 24, 2009 8:43 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** RE: Follow-up questions to your Type A-Briefing Document

Hello Michelle,

Thanks for the following up on the pediatric study. The team is aware of the July 17th start date, and we will have some information by the end of next week.

In addition to what was previously sent, we have the following request:  
For the group of all Phase 3 trials, including main trial and extension data, please provide the number and percentage of patients who had:

- A baseline calcitonin of  $\leq$ ULN and any post-baseline calcitonin  $\geq$ 20 ng/L.**
- A baseline calcitonin of  $<$ 10 ng/mL and any post-baseline calcitonin  $\geq$ 20 ng/L.**
- A baseline calcitonin of  $<$ 20 ng/L and any post-baseline calcitonin  $\geq$ 20 ng/L.**
- A baseline calcitonin of  $\leq$ ULN and a post-baseline calcitonin of  $\geq$ 50 ng/L.**
- A baseline calcitonin of  $<$ 10 ng/mL and any post-baseline calcitonin  $\geq$ 50 ng/L.**
- A baseline calcitonin of  $<$ 50 ng/L and a post-baseline calcitonin of  $\geq$ 50 ng/L.**

Please provide the information by treatment group (LGT, PBO, AC). For the liraglutide group, in addition to providing information for the total liraglutide group, please also provide the information by liraglutide dose.

If you have any questions, please feel free to contact me.

Thanks,  
John

---

From: MTHO (Michelle Thompson) [<mailto:mtho@novonordisk.com>]  
Sent: Tuesday, June 23, 2009 11:34 AM  
To: Bishai, John  
Subject: RE: Follow-up questions to your Type A-Briefing Document

Hi John,

We are working on providing responses to the below questions by tomorrow. Also, have you heard back from Clin Pharm regarding the pediatric pk study? We are anxious to hear back regarding the submitted protocol as there is a scheduled study start date of July 17. Please don't hesitate to give me a call if you have any questions for me. Thank you.

Michelle

---

From: Bishai, John [<mailto:John.Bishai@fda.hhs.gov>]  
Sent: Tuesday, June 23, 2009 8:57 AM  
To: MTHO (Michelle Thompson)  
Subject: Follow-up questions to your Type A-Briefing Document

Hello Michelle,

In your Type A-briefing document, on serial page 133, Table 35 appears to show that a large percentage of patients had

missing values for calcitonin category shifts from baseline to Week 104. Can you please clarify by providing the following information:

1. At Weeks 52 and Weeks 104, how many total patients (regardless of whether they had a calcitonin measurement) were remaining in each treatment group (liraglutide, placebo and active comparator)?
2. How many liraglutide-, placebo-, and active-comparator-treated patients who completed 52 weeks and 104 weeks of study medication had missing calcitonin data at those timepoints? What are the reasons for the missing calcitonin data? Is it possible to obtain calcitonin values for these patients using stored blood samples, if needed?
3. How do pharmacokinetic exposures to the 3.0 mg liraglutide dose in the obese population compare to pharmacokinetic exposures to the 1.8 mg liraglutide dose in the diabetic population?

We ask that you please provide answer to the aforementioned by COB Wednesday. If you have any questions, please feel free to contact me.

Regards,  
John

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/s/

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John M Bishai  
7/23/2009 02:50:53 PM  
CSO

## Bishai, John

---

**From:** Bishai, John  
**Sent:** Wednesday, May 13, 2009 3:01 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** A few questions regarding Liraglutide

Hello Michelle,

We have a few questions in regards to the recent fax which received and a follow-up question to the recent Advisory Committee (AC) meeting. Our questions are listed below:

1. We received your fax on 13 May 2009 regarding a liraglutide-treated patient with "suspected pheochromocytoma" and "suspected formation in thyroid gland". Please provide further clinical history, imaging results, surgical pathology reports, calcitonin values, and RET proto-oncogene typing for this patient.
2. In your Integrated Summary of Safety in your original NDA submission, in the sections regarding laboratory data, you discuss analyses of the number of subjects who develop "clinically significant" values for hematology, chemistry and urinalysis parameters. Is there a table in the ISS which gives the exact values that you designated as "clinically significant" for the various laboratory parameters?
3. At the recent Advisory Committee meeting, members of the AC expressed interest in whether analyses of cardiovascular event rates were done separately for those patients who had had diabetes for  $\geq 10$  years, and those who had had diabetes for  $< 10$  years. Do you plan to do such analyses? If so, what analysis method(s) do you intend to use?

If you have any questions, please feel free to contact me.

Thanks,  
John

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/s/

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John M Bishai  
7/23/2009 02:54:31 PM  
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**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Monday, July 13, 2009 2:35 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** Human Factors study

Hello Michelle,

Thanks for taking my call. As I mentioned over the phone, there are some concerns with the pen's labeling and the possible confusion which may arise from \_\_\_\_\_ My point of mentioning this is to you at this point in time is to make you aware of the possibility of having to conduct a Human Factors study to assess the pen's safety. Specifically, the test may have to assess the potential risk of user interaction with the subject device and the labeling. For additional guidance on human factors, please refer to the Guidance for Industry and FDA Premarket and Design Control Reviewers - Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (<http://www.fda.gov/cdrh/humfac/1497.html>). **b(4)**

If you have any questions, please feel free to contact me.

Regards,  
John



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/s/

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John M Bishai  
7/23/2009 02:56:21 PM  
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## Bishai, John

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**From:** Bishai, John  
**Sent:** Monday, May 18, 2009 2:19 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** A request for NDA 22-341

Hello Michelle,

I hope you are doing well. Can you please provide the number and percentage of patients who had any elevation of blood bilirubin to 2 times the upper limit of normal, 3x ULN and 10x ULN, by treatment, for all Phase 3 trials of liraglutide. Please include treatment groups of LGT 0.6 mg, LGT 1.2 mg, LGT 1.8 mg, placebo, and active control.

Thanks,  
John

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/s/

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John M Bishai  
7/23/2009 02:43:09 PM  
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**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Tuesday, July 14, 2009 9:36 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** Follow-up to our earlier bilirubin Request

Hello Michelle,

I have a follow-up question to our earlier request for bilirubin data. On 28 May 2009, you stated that no patients in the Phase 3 trials had bilirubin elevations  $\geq 2x$  ULN. However, it appears that at least two patients had bilirubin elevations  $\geq 5x$  ULN (Patients 579006 and 761016). Can you please re-query your database to make sure there are not other cases, per our previous request?

Thanks,  
John

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/s/

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John M Bishai  
7/23/2009 02:44:28 PM  
CSO

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Tuesday, June 16, 2009 9:06 PM  
**To:** MTHO (Michelle Thompson)  
**Subject:** Questions for NDA 22-341

Hello Michelle,

We have the following questions

1. In our recent Type A meeting you presented a slide entitled "Liraglutide vs. Exenatide: HbA1c change over 26 weeks (Study 1797)", does the data in this slide and the 14 week extension represent subjects who have completed the study? Please clarify. In addition, we ask that you please provide an ITT-LOCF analysis.
2. We received a case report (submitted to IND 61040) on 10 Jun 2009 regarding a patient with C-cell hyperplasia who had testing done for RET proto-oncogene mutations. Was this testing done on blood or on hyperplastic thyroid tissue?

If you have any questions, please let me know.

Thanks,  
John

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/s/

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John M Bishai  
7/23/2009 02:45:57 PM  
CSO

## **Bishai, John**

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**From:** Bishai, John  
**Sent:** Thursday, June 04, 2009 1:44 PM  
**To:** MTHO (Michelle Thompson)  
**Subject:** A couple of non-clinical questions

Hello Michelle,

It was nice to meet you the other day. Like yourself, I am working on the meeting minutes and should have some meeting specific questions for you. In the mean time, could you please provide answers to the following non-clinical questions:

1. Based on levels of impurities specified in drug substance and drug product acceptance criteria, provide a tabulated summary of data showing toxicity of impurities and degradation products was adequately assessed in repeat dose and genetic toxicity studies. This tabulated summary should include current drug substance acceptance criteria for each impurity, the drug batch used to qualify the impurity, the level of impurity in the batch used for qualification, and report numbers for repeat dose and in vitro genetic toxicity studies qualifying each impurity or groups of impurities. If there are any reactive impurities or impurities with a structural alert for genetic toxicity, you should report the data for that impurity separately.
2. Please submit historical control data for embryofetal development toxicity studies of liraglutide in rats and rabbits from the research facility that performed definitive studies. Historical control data should be provided for every finding in liraglutide treated groups, regardless of whether or not it was considered treatment-related. Historical control group data should include 5 consecutive years of data and it should include historical control group data from the year the study was performed.

Thanks,  
John



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/s/

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John M Bishai  
7/23/2009 02:52:15 PM  
CSO

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Monday, June 29, 2009 2:31 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** Corrected information for the Liraglutide Type A meeting

Hello Michelle,

It was nice speaking to you, and as I mentioned during our conversation we would like to you please submit a corrected copy of the briefing document for the Type A meeting that was held 1 Jun 2009. We are finding it difficult to reconcile the two sets of errata that were submitted on 25 Jun 2009 with the original briefing document. Please include updated tables that reflect the re-analyses done after the programming error that was reported on 25 Jun 2009. If text or figures are affected by the reanalysis, please correct those, also. Additionally, if any of the figures from your slide presentation from 1 Jun 2009 were produced from analyses that were affected by the programming error, please submit a corrected set of slides.

Thanks,

John

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/s/

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John M Bishai  
7/23/2009 02:48:20 PM  
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**NDA Amendment**



July 20, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza [liraglutide injection]  
NDA Amendment: Revised Labeling (Carton, Container, Instructions for Use, and  
Physician Insert)**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the July 10, 2009 telephone conversation with John Bishai, Regulatory Project Manager, in which it was agreed that revised labeling and samples of the pens would be submitted.


As requested by the Division, two samples of \_\_\_\_\_ the pen presentations were sent today to John Bishai's attention via FedEx to:

b(4)

Building 22, Room 3239  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Additionally, in order to aid in the Division's understanding of the pen presentations included in the NDA, below is a clear listing of which pens will be marketed and which ones will be available for sampling:

**Trade Presentations**

- - 
  - 
  -
- 

b(4)

**Sample Presentations**

- -
- 

b(4)

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

The carton and container labels have been designed so that patients, physicians and pharmacists can easily distinguish between the various pen presentations.

Novo Nordisk intends to market \_\_\_\_\_

b(4)

At this time we are providing the following revised labeling as an amendment to NDA 22-341:

- Cartons
- Container Labels
- Business Reply Card
- Physician Insert
- Instructions for Use for the pen

This submission is being provided electronically (approximately 5 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5668 created on July 16, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.07.20 08:58:18 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

**NDA Amendment**



July 20, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated July 16, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the July 16, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This amendment is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5668 created on July 16, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Sincerely,

NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary  
Ann McElligott**

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.07.20 09:03:18 -04'00'

Mary Ann McElligott, Ph.D.

Associate Vice President, Regulatory Affairs

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Princeton, NJ 08540

609-987-5800 phone

[www.novonordisk-us.com](http://www.novonordisk-us.com)

**NDA Amendment**



July 17, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA requests for information dated July 14, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the July 14, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. One of the July 14<sup>th</sup> requests was for serum creatinine levels from Phase 2 and Phase 3; the Phase 3 data is provided in this amendment and the Phase 2 data will be provided shortly.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5674 created on July 12, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)



Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary  
Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=loko@novonordisk.com  
Date: 2009.07.17 09:01:03 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

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100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

Sincerely,  
NOVO NORDISK INC.  
Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.07.08 11:57:57 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

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609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>CDER OSE Consults</b> <b>Mildred Wright</b> <b>Office of Safety and Epidemiology</b> <b>Email: <a href="mailto:mildred.wright@fda.hhs.gov">mildred.wright@fda.hhs.gov</a></b> <b>WO22 RM 4492, Phone: 796-1027</b>		FROM: <b>John Bishai, Ph.D.</b> <b>Regulatory Project Manager</b> <b>DMEP, HFD-510, Phone: 796-1311</b>		
DATE July 16, 2009	IND NO.	NDA NO. 22,341	TYPE OF DOCUMENT REMS/Medguide	DATE OF DOCUMENT July 8, 2009
NAME OF DRUG Victoza (liraglutide injection)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Treatment of Type II Diabetes	DESIRED COMPLETION DATE August 12, 2009	
NAME OF FIRM: Novo Nordisk				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
This is a consult request for a REMS and MedGuide review. The documents are in the EDR, direct links are below: Cover Letter: <a href="#">\\cdsesub1\evsprod\NDA022341\0039\m1\us\102-cover-letters\cover.pdf</a> MedGuide (WORD): <a href="#">\\cdsesub1\evsprod\NDA022341\0039\m1\us\114-labeling\1141-draft\proposed-med-guide.doc</a> MedGuide (PDF): <a href="#">\\cdsesub1\evsprod\NDA022341\0039\m1\us\114-labeling\1141-draft\proposed-med-guide.pdf</a>				
SIGNATURE OF REQUESTER John Bishai		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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John M Bishai  
7/16/2009 12:57:11 PM

## NDA Amendment



July 8, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341**  
**Victoza [liraglutide injection]**  
**NDA Amendment: Revised Information Package from June 1, 2009 FDA Meeting**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also make reference to the:

- June 1 Type A meeting Information Package submitted on May 18, 2009
- Type A meeting held with the Division on June 1, 2009
- June 25, 2009 NDA Amendments with corrected calcitonin shift tables

On June 29, 2009 an e-mail was received from John Bishai, Regulatory Project Manager, requesting a revised copy of the May 18, 2009 Information Package incorporating the corrected calcitonin shift tables and a revised June 1<sup>st</sup> Power Point presentation. At this time Novo Nordisk is providing the revised Information Package with the corrected calcitonin data incorporated (Module 1.6.2) and the revised Power Point presentation (Module 1.6.3).

The revised Information Package also includes a summary of a recently completed study "*Study of the Acute Effects on Plasma Calcitonin after a Single Subcutaneous Administration in Fasted GLP-1-Receptor Knock-out Mice and CD-1 Mice*" which shows that liraglutide does not increase calcitonin in knock-out mice.

Additionally the 2 year time point is available for the obesity trial NN8022-1807, one year data from this trial was shown at the June 1 meeting. This data also demonstrates no effect on calcitonin after 2 years of treatment and at a higher dose than was utilized in the diabetes development program.

We also are including two publications that bear directly on issues discussed at the June 1<sup>st</sup> Type A Meeting. One publication is the editorial in Lancet that accompanied the publication of the results from trial 1797, the direct comparison of liraglutide vs exenatide. The second

**Novo Nordisk Inc.**  
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Princeton, NJ 08540  
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is a publication about which Dr. Parola expressed interest that describes the GLP-1/bone axis in mice and supports the critical role of GLP-1 in modulating calcium turnover in rodents.

- Editorial published in June 2009 *Lancet* entitled “*GLP-1 receptor agonists for type 2 diabetes*” De Block C, Van Gaa L (Appendix VII). The authors give their view on the liraglutide head-to-head study versus exenatide (NN2211-1797) and their recommendation for no calcitonin screening in the general population.
- November 2007 article from *Endocrinology* entitled “*The Murine Glucagon-Like Peptide-1 Receptor Is Essential for Control of Bone Resorption*” Yamada C, Yuichiro Y, et al., (Appendix VIII). This article was discussed with the Division at the June 1<sup>st</sup> meeting.

Please note that the revised Information Package has also been updated with final draft protocols for the Cardiovascular Outcomes study, Prospective Claims i3 Aperio study and Medullary Thyroid Cancer Registry; these are provided in Appendices III – V. The proposed REMS and Medication Guide requested by the Division on July 1<sup>st</sup> will be submitted under separate cover.

As an additional follow-up to the June 1 meeting discussion, we are pleased to inform you that we received European Commission approval for Victoza on June 30. As discussed at the meeting Novo Nordisk is committing to conduct a global post-approval cardiovascular outcomes study in approximately 9000 patients. With the approval in the EU, we have a post-approval commitment to submit the final protocol for the cardiovascular study by December 31, 2009. To assure that this study meets global regulatory requirements, we are seeking input on the design from different health authorities. Therefore, in order to meet the EU filing deadline and to allow adequate time for internal processes, we would appreciate feedback from the Division on the protocol by August 8, 2009.

This submission is being provided electronically (approximately 9 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5667 created on July 5, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

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**NDA AMENDMENT  
PROPOSED REMS AND MEDICATION GUIDE**



July 8, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Proposed REMS and Medication Guide**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the July 1, 2009 request from FDA Project Manager, John Bishai, for the draft Medication Guide and REMS documents.

At this time, Novo Nordisk is providing the following proposals as an Amendment to NDA 22-341:

- REMS
- REMS Supporting Document
- Medication Guide

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.5.0, virus definition file version 5667 created on July 5, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

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Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
**Ann McElligott**

Digitally signed by Michelle Thompson  
on behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo  
Nordisk Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.07.08 12:00:35 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs  
Novo Nordisk Inc.  
609-987-5831 (direct)  
mamc@novonordisk.com

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

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NDA Amendment



June 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA requests for information dated June 23<sup>rd</sup>  
(Question 1 and 2) and June 24, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the June 23 and June 24, 2009 requests from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information for the June 23<sup>rd</sup> (Question 1 and 2) and June 24<sup>th</sup> requests as an Amendment to NDA 22-341. This same amendment was sent via e-mail to Dr. Bishai on June 24, 2009.

This submission is being provided electronically (approximately 6 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5653 created on June 21, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on behalf  
of Mary Ann McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory Affairs, email=loko@novonordisk.com  
Date: 2009.06.25 09:47:32 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

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NDA Amendment



June 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated June 16, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the June 16, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. This same amendment was sent via e-mail to Dr. Bishai on June 24, 2009.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5653 created on June 21, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on**  
**behalf of Mary Ann**  
**McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory Affairs, email=loko@novonordisk.com  
Date: 2009.06.25 08:35:29 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



June 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated June 23, 2009 (Question 3)**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the June 23, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information for Question 3 as an Amendment to NDA 22-341. This same amendment was sent via e-mail to Dr. Bishai on June 24, 2009.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5653 created on June 21, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Lois Kotkoskie on behalf  
of Mary Ann McElligott

Digitally signed by Lois Kotkoskie on behalf of Mary  
Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=loko@novonordisk.com  
Date: 2009.06.25 08:37:45 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

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**NDA Amendment**



June 22, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated June 4, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the June 4, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5649 created on June 17, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory Affairs, email=loko@novonordisk.com  
Date: 2009.06.22 13:05:24 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

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## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):

John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE 6/3/2008	IND NO. 22-341	NDA NO. N/A	TYPE OF DOCUMENT RMP Review	DATE OF DOCUMENT May 23, 2008
NAME OF DRUG Victoza (liraglutide injection)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic agent	DESIRED COMPLETION DATE January 15, 2009

NAME OF FIRM: Novo Nordisk

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the RMP for NDA 22-341. The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.  
Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

-----  
John M Bishai  
6/5/2008 11:56:00 AM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
6/3/2008

IND NO.  
22-341

NDA NO.  
N/A

TYPE OF DOCUMENT  
Trade Name Review  
Request

DATE OF DOCUMENT  
May 23, 2008

NAME OF DRUG  
Victoza (liraglutide  
injection)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
August 25, 2008

NAME OF FIRM: Novo Nordisk

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the trade name for NDA 22-341. The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.  
Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND



PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

-----  
John M Bishai  
6/5/2008 11:57:46 AM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):

John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE 6/3/2008	IND NO. 22-341	NDA NO. N/A	TYPE OF DOCUMENT RMP Review	DATE OF DOCUMENT May 23, 2008
NAME OF DRUG Victoza (liraglutide injection)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic agent	DESIRED COMPLETION DATE January 15, 2009

NAME OF FIRM: Novo Nordisk

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the RMP for NDA 22-341. The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.  
Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

-----  
John M Bishai  
6/5/2008 11:53:58 AM

# REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE 6/3/2008	IND NO. 22-341	NDA NO. N/A	TYPE OF DOCUMENT Patient Labeling Review	DATE OF DOCUMENT May 23, 2008
NAME OF DRUG Victoza (liraglutide injection)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic agent	DESIRED COMPLETION DATE January 15, 2009

NAME OF FIRM: Novo Nordisk

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This a request for a Patient labeling review (ie PPI, User Manuals, etc.) . The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.  
Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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John M Bishai  
6/4/2008 04:22:37 PM



**REQUEST FOR CONSULTATION**

TO (Office/Division): IRT QT Review Group  
Devi Kozelli  
OND/O DEI/DCRP  
devi.kozeli@fda.hhs.gov  
WO22 RM4183/ Phone: X6-1128

FROM (Name, Office/Division, and Phone Number of Requestor): John Bishai  
Division of Metabolism and Endocrinology Products,  
301-796-1311

DATE  
6/3/2008

IND NO.  
22-341

NDA NO.  
N/A

TYPE OF DOCUMENT  
Clinical Information  
Amendment - QT  
Protocol

DATE OF DOCUMENT  
May 23, 2008

NAME OF DRUG  
Victoza (liraglutide  
injection)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
January 15, 2009

NAME OF FIRM: Novo Nordisk

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

**II. BIOMETRICS**

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

**III. BIOPHARMACEUTICS**

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

**IV. DRUG SAFETY**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the clinical study reports for NDA 22-341. The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.  
Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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/s/

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John M Bishai  
6/4/2008 04:25:09 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER/OPS  
**Jim McVey**  
 james.mcvey@fda.hhs.gov  
 Microbiologist  
 New Drug Microbiology  
 WO51 Room # 4162 phone: x615723

FROM (Name, Office/Division, and Phone Number of Requestor):  
**John Bishai Ph.D.**  
 Regulatory Project Manager  
 DMEP, HFD-510, phone #: 6-1311

DATE  
6/3/2008

IND NO.  
22-341

NDA NO.  
N/A

TYPE OF DOCUMENT  
Original NDA

DATE OF DOCUMENT  
May 23, 2008

NAME OF DRUG  
**Victoza (liraglutide injection)**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Anti-diabetic agent**

DESIRED COMPLETION DATE  
**January 15, 2009**

NAME OF FIRM: **Novo Nordisk**

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This a micro request to check the sterility of the product. The document can be found in the EDR (see link below). This particular NDA was previously IND 61,040. Please note this drug is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1.

Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\0000

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

-----  
John M Bishai  
6/4/2008 04:20:06 PM



NDA 22-341

**NDA ACKNOWLEDGMENT**

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

Dear Dr. McElligott:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Victoza (liraglutide injection)

Date of Application: May 23, 2008

Date of Receipt: May 23, 2008

Our Reference Number: NDA 22-341

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 July 22, 2008, 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/oc/datacouncil/spl.html>. 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 be in the Prescribing Information (physician labeling rule) format.

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/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology  
Products  
Center for Drug Evaluation and Research  
Food and Drug Administration



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/s/

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John M Bishai  
6/3/2008 09:51:33 AM

**NDA Amendment**



May 28, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Amundson Avenue  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated May 18, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the May 18, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5625 created on May 24, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory Affairs, email=loko@novonordisk.com  
Date: 2009.05.28 13:15:01 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



May 22, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Amundson Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated May 13, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the May 13, 2009 request from FDA Project Manager, John Bishai.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5618 created on May 17, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson**  
on behalf of Mary Ann  
McElligott

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
com  
Date: 2009.05.22 11:14:04 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

## INFORMATION PACKAGE



May 18, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341**  
**Victoza [liraglutide injection]**  
**Type A Information Package**

Dear Dr. Parks:

Please refer to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. We also refer to the Type A meeting which is scheduled for Monday, June 1<sup>st</sup> 2009 from 3:00 – 4:00 PM as arranged through John Bishai, Regulatory Project Manager.

The Information Package for the scheduled meeting is being provided under cover of this letter. The package contains a final list of questions for Division input and feedback, and background information to further facilitate discussion. We have taken Division input and guidance on meeting focus as outlined in John Bishai's May 11, 2009 email, and believe that we have provided sufficient background information in the package to facilitate an in depth discussion on liraglutide's benefit:risk profile. Specifically, the package outlines liraglutide's unique efficacy and safety advantages relative to other approved therapies, discusses potential risk (including medullary thyroid cancer) and our proposal for monitoring and managing these risks in post-approval clinical trials and in the general population. Based on the content of the package and our discussion at the meeting, we hope to come to agreement with the Division on a path forward regarding approvability during this review cycle.

Additionally, as requested, 20 desk copies are also being provided, via courier to John Bishai's attention. A final list of Novo Nordisk attendees will be provided shortly before the meeting. We would appreciate your written responses to the meeting questions as soon as possible to allow for more focused discussion.

This submission is being provided electronically (approximately 5 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

definition file version 5614 created on May 13, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US,  
o=Novo Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2009.05.18 12:35:28 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-341

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 file for your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection

We also refer to your April 22, 2009, correspondence requesting a Type A meeting to discuss an adequate Risk Management Plan for liraglutide. This letter is in follow-up to the email I sent to Michelle Thompson on May 5, 2009 notifying her that the meeting had been granted and scheduled.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

**Date:** Monday, June 1, 2009  
**Time:** 3:00 to 4:00 PM  
**Location:** FDA White Oak Campus  
10903 New Hampshire Ave.  
Building 22  
Silver Spring, MD 20993-0002

CDER Participants (tentative):

Office of Drug Evaluation II (ODE-II)  
Curtis Rosebraugh, M.D., M.P.H. Director

Division of Metabolism and Endocrinology (DMEP)  
Mary Parks, M.D. Director  
Amy Egan, M.D., M.P.H. Deputy Director for Safety  
Hylton Joffe, M.D., M.M.Sc. Diabetes Clinical Team Leader  
Karen Mahoney, M.D. Clinical Reviewer  
Lisa Yanoff, M.D. Clinical Reviewer  
Karen Bruno-Davis, Ph.D. Pharmacology/Toxicology Supervisor

Anthony Parola, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D., M.S.	Chief, Project Management Staff
John Bishai, Ph.D.	Regulatory Project Manager

Office of Clinical Pharmacology (OCP)

Wei Qiu, Ph.D.	Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer

Office of Biometrics (OB)

Todd Sahlroot, Ph.D.	Biometrics Team Leader and Deputy Division Director
Janice Derr, Ph.D.	Biometrics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Suong Tran, Ph.D.	Product Assessment Lead
Joseph Leginus, Ph.D.	Chemistry Reviewer

Office of Surveillance and Epidemiology (OSE)

Cheryl Campbell, M.S.	Chief, Project Management Staff
Millie Wright	Regulatory Project Manager

OSE-Division of Risk Management

Mary Dempsey	Risk Management Coordinator
Kendra Worthy	Risk Management Analyst

OSE- Division of Medication Error Prevention and Analysis

Carlos Mena-Grillasca	Safety Evaluator
Walter Fava	Safety Evaluator
Kellie Taylor, Pharm.D.	Team Leader

Please have all your attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at [john.bishai@fda.hhs.gov](mailto:john.bishai@fda.hhs.gov) so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: John Bishai at extension x1311.

Provide the background information for the meeting (three copies to the application and twenty desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by May 18, 2009, we may cancel or reschedule the meeting.

NDA 22-341

Page 3

If you have any questions, call me at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration



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/s/

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John M Bishai  
5/13/2009 05:53:54 PM

## MEMORANDUM OF TELECON

DATE: May 5, 2009

APPLICATION NUMBER: NDA 22-341

**BETWEEN:**

Name: Alan Moses, M.D.  
Mary Ann McElligott, Ph.D.  
Michelle Thompson  
Milan Zdravkovic, M.D., Ph.D.  
Peter Bonne Eriksen

Phone: PHONE 1-888-529-0349 x606304  
Representing: Novo Nordisk, Inc.

**AND**

Name: Hylton Joffe, M.D., M.M.Sc.  
Karen Mahoney, M.D.  
John Bishai, Ph.D.  
DIVISION OF METABOLISM AND ENDOCRINOLOGY, HFD-510

**SUBJECT:** POSSIBLE CALCITONIN DATA ANALYSES FOR THE BRIEFING PACKAGE FOR THE UPCOMING TYPE A MEETING FOR LIRAGLUTIDE.

**BACKGROUND:**

Recently, this application went to an Advisory committee on April 2nd to discuss cardiovascular and thyroid safety. Liraglutide was found to be associated with thyroid C-cell tumors in rats and mice at clinically relevant exposures. Extensive discussion occurred regarding the clinical significance of these animal findings, and regarding the challenges of addressing this finding in human clinical trials. The committee's vote was split regarding the approvability of liraglutide in light of this safety concern. A Type A meeting is now planned with the applicant for further discussions. Novo requested a premeeting teleconference to discuss calcitonin analyses for the meeting briefing document.

**DISCUSSION:**

During the discussion, Novo Nordisk informed the Division that they are pooling together additional data supporting what they feel is a the lack of effect of liraglutide on calcitonin and on human tumor risk. On June 1, 2009, Novo Nordisk will present data from two studies: a 2 yr extension study and a 26-week comparative study-liraglutide vs. exenatide.

Afterwards, the discussion focused on previously submitted shift tables and the ability to identify

outliers within the data set. Specifically, Dr. Joffe asked the applicant to present data for those patients who had persistently elevated calcitonin levels. Dr. Joffe also suggested that the applicant use a lower cut-off in shift tables, e.g. 1.5 times the upper limit of normal.

Dr. Mahoney discussed the possibility that some of the calcitonin effect might be due to effects of liraglutide on insulin and glucose levels rather than a specific drug effect per se. She suggested explorations for correlations between changes in insulin and glucose levels and changes in calcitonin. If insulin values are not available, explorations could occur by drug class, e.g. the effect of comparator agents that increase insulin levels vs those that do not. The applicant responded that they would attempt some of these types of analyses, but that there might not be adequate time prior to the meeting.

During the discussion, the applicant was asked about their plans to submit efficacy data from a head-to-head study comparing liraglutide and exenatide. The applicant stated that they plan to submit a summary of these data with the meeting package, but that they do not think there will be time to submit the full study report prior to the meeting. The applicant is aware that the Agency is interested to know if there is a unique benefit to liraglutide beyond its once a day injection schedule. This will be important in a risk:benefit analysis, given the drug's safety concerns.

As part of the discussion, Drs. Mahoney and Joffe felt that it was important to reiterate the purpose of the upcoming meeting. The applicant was informed that the intent of the meeting was to permit the applicant to provide an updated presentation on their view of the safety data, and on any unique efficacy benefits, of liraglutide. After the meeting, there will be further internal Agency discussions prior to a decision regarding approvability.

The applicant asked Drs. Joffe and Mahoney to review the questions the applicant had submitted with their meeting request, and to provide some feedback regarding how Novo should prioritize their efforts in choosing topics to include in their meeting packet. A subsequent email (attached) was sent to the applicant with further guidance on the Agency's expectation of the meeting content.

(\*\*attach email\*\*)

---

John Bishai, Ph.D.  
Regulatory Project Manager

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Monday, May 11, 2009 11:14 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** MAMC (Mary Ann McElligott)  
**Subject:** Priorities for the upcoming meeting

Hello Michelle,

During our teleconference last Tuesday, one of the topics of discussion was defining the priorities for the upcoming Type A meeting. After further internal discussion, the division felt that it would benefit both parties to reiterate the focus of the meeting and to provide some guidelines. In summary, the purpose of the upcoming meeting is for Novo to give its best rationale for why Novo thinks that liraglutide could be approved in this cycle, despite safety concerns that were discussed at the recent Advisory Committee meeting. We would expect to see a robust demonstration of favorable benefit: risk before considering approval. Topics of interest include Novo's updated perspective on:

- The preclinical signal of C-cell tumors
- Human thyroid cancer risk and the challenges of detecting medullary thyroid cancer in clinical trials
- The challenges of and need for monitoring for thyroid cancer risk in humans treated with liraglutide
- Pancreatitis risk
- Any unique efficacy or safety advantages that liraglutide has relative to other available therapies, with emphasis on head-to-head comparisons where the comparator was administered at full clinical doses.

The meeting package should contain a thorough discussion of the above topics, and we expect that they will comprise the majority of the meeting discussion. After the meeting, the Agency expects to use the data contained in the meeting package and data presented at the meeting for further internal discussion regarding the approvability of liraglutide in this review cycle.

The meeting package should also contain a preliminary Risk Management Plan that would outline Novo's proposals for adequately monitoring and mitigating risk, in the event that liraglutide is approved this cycle.

If you have any questions, please feel free to contact me.

Regards,  
John

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: john.bishai@fda.hhs.gov  
Tel: 301.796.1311  
Fax: 301.796.9712

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/s/

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John M Bishai  
5/12/2009 04:06:18 PM  
CSO

## Bishai, John

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**From:** Bishai, John  
**Sent:** Tuesday, May 05, 2009 4:05 PM  
**To:** MTHO (Michelle Thompson)  
**Cc:** Aljuburi, Lina  
**Subject:** Type A meeting for Liraglutide

Hello Michelle,

I tried scheduling the type A meeting for June 2nd as per our conversation. Unfortunately, I was not able to make it work due to many conflicts. However, I was able to schedule the meeting late in the day on the 1st.

**Meeting:** Type A Meeting  
**Sponsor:** Novo Nordisk  
**Drug:** Victoza (liraglutide)  
**Date:** June 1, 2009  
**Time:** 3:00-4:00pm

A formal meeting acceptance letter will be sent to you shortly. If you have any questions, please let me know.

Thanks,  
John

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/s/

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John M Bishai

5/8/2009 02:04:09 PM

Type A meeting was accpeted on May 5, 2009

NDA Amendment



May 8, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated April 17, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the:

- March 5, 2009 request received from FDA for responses to deficiencies cited during the January 2009 analytical site inspections conducted at \_\_\_\_\_ the March 27, 2009 response from Novo Nordisk. **b(4)**
- March 25, 2009 request from FDA for responses to deficiencies cited during the January 2009 analytical site inspections conducted at Lund University Hospital in Lund, Sweden and the March 30, 2009 response from Novo Nordisk.
- April 17, 2009 request from FDA for a summary of the pivotal bioequivalence and other clinical pharmacology studies including a by-study summary of the percentage of duplicate values in the analytical standards and listing of subject IDs for each study for which these criteria were used.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. As agreed upon at the January 2009 inspection conducted at \_\_\_\_\_ the bioanalytical report for the analytical determination of liraglutide in plasma samples has been updated. The report is available upon request. **b(4)**

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5607 created on May 6, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.



Sincerely,

NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary  
Ann McElligott**

Digitally signed by Lois Kotkoskie on  
behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk  
Inc, ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.05.08 11:14:27 -04'00'

Mary Ann McElligott, Ph.D.

Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



Henrik Rasmussen, M.D.  
Vice President, Clinical Development, Medical & Regulatory Affairs  
Novo Nordisk, Inc.  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Rasmussen:

Between December 1 and 11, 2008, Ms. Dorothy Denes, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct as the sponsor of the following clinical investigations of the investigational drug Liraglutide (Victoza):

- A. NN2211-1573 entitled "Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimpiride in Type 2 Diabetes (A Fifty-Two Week [with Fifty-Two Week Open-Label Extension] Double-Blind, Multicenter, Randomized, Parallel Study to Investigate Safety and Efficacy)"
- B. NN2211-1574 entitled "Liraglutide Effect and Action in Diabetes (LEAD-4): Effect on Glycemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

We are aware that at the conclusion of the inspection, Ms. Denes presented and discussed with you Form FDA 483, Inspectional Observations.

From our evaluation of the establishment inspection report, the documents submitted with that report, and your letters of December 17, 2008 and February 26, 2009 written in response to the Form FDA 483, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Denes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief, Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Bldg. 51, Rm. 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

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/s/

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Constance Lewin  
4/24/2009 12:05:52 PM

## REQUEST FOR TYPE A MEETING



April 22, 2009

Mary Parks, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 22-341  
Victoza [liraglutide injection]  
Type A Meeting Request**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the:

- April 2, 2009 Endocrine and Metabolism Drugs Advisory Committee Meeting
- April 3, 2009 telephone conversation between Dr. Mary Parks, Division Director, and Dr. Mary Ann McElligott, Novo Nordisk regarding interactions with FDA
- April 7, 2009 e-mail from John Bishai, Regulatory Project Manager, regarding submission of the Type A meeting request
- April 22, 2009 e-mail from Dr. Mary Parks, Division Director, stating the Division would be willing to grant a meeting

Based on the outcome of the Advisory Committee and the panel's recommendations to the Division, Novo Nordisk is requesting a Type A meeting with the Agency. The primary purpose of this meeting is to discuss and agree on appropriate Risk Management activities to support the path forward for liraglutide. We will present and discuss additional long-term clinical data that support the safety and sustained benefits of liraglutide. The required information (including a draft list of questions) to support this meeting request is provided. More detailed documentation will be provided 2 weeks prior to the agreed upon meeting date.

We propose the dates of May, 26, 27, or 28, 2009 (morning preferable) for the meeting. Representation from Division Management, Medical, and representative appropriate for risk management discussions is requested. We would propose that the Agency include Dr. Michael Tuttle, who was the thyroid specialist at the April 2 meeting invited to provide input on managing the risks. Approximately eight to ten participants from Novo Nordisk representing Research and Development will attend the meeting. Additional participants

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
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may attend based on the FDA attendees or issues raised after the review of the pre-meeting package. Please provide a list of FDA attendees when available.

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Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

Michelle Thompson  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on  
behalf of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of  
Mary Ann McElligott, c=US, o=Novo Nordisk  
Inc, ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.04.22 15:54:11 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

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**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

NDA Amendment



April 17, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated April 7, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the:

- waiver (Module 1.9.1) and deferral (Module 1.9.2) for pediatric studies submitted in the original NDA on May 23, 2008
- protocol synopsis for study NN2211-3659 "*Effect of liraglutide in combination with metformin versus metformin monotherapy on glycemic control in children and adolescents with type 2 diabetes: A 16 week double-blind parallel group multi-centre study followed by a 36 week open-label extension*" submitted in the original NDA on May 23, 2008.
- protocol for study NN2211-1800 "*A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Pediatric (10 – 17 years old) and Adult Subjects with Type 2 Diabetes*" submitted on February 26, 2009 to both the NDA (Sequence Number 0026) and IND 61,040 (Serial Number 0329).
- April 7, 2009 request received from John Bishai, FDA Project Manager, for information on the proposed pediatric studies.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. Novo Nordisk is also providing a revised protocol synopsis for study NN2211-3659.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5585 created on April 15, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Senior Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.04.17 13:41:44 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

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NDA Amendment



March 30, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated March 25, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the March 25, 2009 request from FDA for responses to specific infractions cited during the January 2009 analytical site inspections conducted at Lund University Hospital in Lund, Sweden.

At this time, Novo Nordisk is providing the following in response to your March 25<sup>th</sup> letter:

- o Attached is the site response (Lund University Hospital) that was sent to Dr. Viswanathan, Division of Scientific Investigators, on February 8, 2009.
- o In response to your recommendation for re-evaluation of the 1692 data, please refer to our March 27, 2009 NDA Amendment.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5564 created on March 25, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Lois Kotkoskie on  
behalf of Mary  
Ann McElligott

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.03.30 12:04:58 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



March 27, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated March 5, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the March 5, 2009 request received from Lina AlJuburi, FDA Project Manager, for responses to deficiencies cited during the January 2009 analytical site inspections conducted at the \_\_\_\_\_

b(4)

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5530 created on February 19, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

Lois Kotkoskie on  
behalf of Mary Ann  
McElligott

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, o=US, ou=Novo Nordisk Inc, ou=Regulatory Affairs, email=lkko@novonordisk.com  
Date: 2009.03.27 15:48:25 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

MEMORANDUM

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

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DATE: February 25, 2009

TO: Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products

THROUGH: C.T. Viswanathan, Ph.D. \_\_\_\_\_  
Associate Director - Bioequivalence  
Division of Scientific Investigations

FROM: Lisa Capron  
Consumer Safety Officer  
Division of Scientific Investigations

SUBJECT: Review of EIR covering NDA 22-341  
Victoza® (liraglutide injection)  
Sponsored by Novo Nordisk A/S Global Development  
Bagsvaerd, Denmark

At the request of Division of Metabolism and Endocrinology Products, the Division of Scientific Investigations audited the clinical portion of the following bioequivalence study. A review of the analytical portions of the study is being provided separately.

**Study# IMP NN2211-1692:** "A Randomized, Double-Blind, Single-Center, Two-Period, Cross-Over Trial in Healthy Subjects Investigating the Bioequivalence Between the Phase 3a Formulating of Liraglutide (Formulation 4) and the Planned Phase 3b Formulation (Final Formulation 4)"

**Clinical Site:** Lund University Hospital, Lund, Sweden

Following the inspection of the site (January 26 - 29, 2009), a 2-item Form 483 item was issued. The evaluation of the significant findings and response letter (February 18, 2009) are as follows:

- 1) Failure of the clinical site to maintain the blinding code to identify that the study formulations administered to the individual subjects followed the randomization code. The

**site was unable to provide assurance that the individual test articles administered to subjects or retained for reserve samples contained a specific formulation.**

On 06/15/07 the site recorded that the envelopes containing the sealed blinding code had been sent back to the sponsor. They did not retain in their possession the original sealed blinding code, and they did not have unblinded study records to verify which formulation was administered to specific subjects at each dosing, or the identities of the reserve samples. Although during the inspection the sponsor emailed a document represented to be the blinding code, the document was generated on 05/22/07, after the conduct of the study. There was no assurance that this code was identical to that provided to the site at randomization. Therefore, the records do not assure the identity of the drug products administered to subjects or the reserve samples.

The protocol for this study stated that "Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure and will be collected by the Monitor." The firm's response letter stated that the sealed codes were handled according to ICH GCP guidelines, section 8.4.6. Please note that Agency's Final Rule and a detailed Guidance put out from DSI for a number of years now, clearly address this issue and we have international compliance on this issue.

- 2) Source data were not signed and dated by the individual collecting the data. For example; collection time points for the pharmacokinetic blood samples were not attributable to either of the two study staff present at the time of collection, corrections to the raw data in 3 of 4 occurrences were performed approximately 3 months after the date of collection and cannot be verified, and those corrections were not performed by the staff present during the collection.

The impact of the missing signatures and dates to the study would have been minimal, except that the site made retrospective changes three months after the fact. Making unverifiable changes to the data is unacceptable. The 3 subject records involved the following samples:

#100006, Visit 2, sample 12, 12 hour  
#100008, Visit 3, sample 18, 16 hour  
#100015, Visit 3, sample 17, 15 hour  
#100015, Visit 3, sample 18, 16 hour

The firm's response letter stated they agreed that the design of the Case Report Forms (CFRs) used to capture the source data was not optimal, as it did not allow the staff collecting the samples to date and sign the collection time. However, they had created a schedule for blood collection time points and that the staff had been instructed to follow that schedule. They stated that the investigator and research coordinator, who had not performed the blood collection task, had evaluated and corrected the source data after receiving a Date Correction Form (DCF) from the sponsor monitor. No corrective actions were purposed by the firm for the significant observation.

**Conclusions:**

Based on the above findings DSI concludes the following:

- There was no assurance of the identity of the drug products administered to subjects or of the reserve samples.
- The firm changed records of blood collection without verification for the study samples identified in Observation #2, above.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Lisa Capron

**Final Classification:**

VAI - Lund University Hospital

cc:

DSI/Vaccari

DSI/Capron/Patague/Rivera-Lopez/CF

OND/ODEII/DMEP/Parks

OND/ODEII/DMEP/Bishai

HFR-PA1500/Gordon

HFR-CE450/Sheehan

Draft: LKC 02/17/09

Edit: MFS 02/19/09

DSI: 5901; O:\BE\eircover\22341LUH.LUN.doc

FACTS: 1000802

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this page is the manifestation of the electronic signature.**  
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/s/  
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Lisa Capron

3/5/2009 01:42:13 PM

CHEMIST

"Dr. Viswanathan signed the paper copy on 03/05/09."

NDA Amendment



February 26, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Pediatric PK Protocol NN2211-1800**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes.

Additional reference is made to IND 61,040 for liraglutide (NNC90-1170), a GLP-1 analog, submitted on October 5, 2000, which is under investigation as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes.

At this time, Novo Nordisk is amending the Preliminary Pediatric Plan submitted with the original NDA with this protocol for the following study (please note that the Pediatric Plan previously contained a synopsis of Study NN2211-1800):

- **Phase 1 NN2211-1800:** “A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Pediatric (10 – 17 years old) and Adult Subjects with Type 2 Diabetes.”

NN2211-1800 is a 2-part trial involving pediatric (age 10 – 17 years) and adult subjects (18 – 45 years) with type 2 diabetes. The primary objective of this study is to assess the safety and tolerability of 0.3, 0.6, 0.9, 1.2 and 1.8 mg doses of liraglutide in the pediatric population (10 – 17 years of age). In addition, the trial is designed to assess the safety and tolerability of liraglutide regimen starting with the 0.6 mg daily dose for one week followed by 1.2 mg daily the next week and ending with 1.8 mg daily (the 3<sup>rd</sup> week) in the pediatric population (10 – 17 years of age).

Please note that Novo Nordisk is also submitting protocol NN2211-1800 to IND 61,040, and is committing not to start the study until July 17, 2009.

This submission is being provided electronically (approximately 1.5 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5534 created on February 23, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).



Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

Lois Kotkoskie on  
behalf of Mary  
Ann McElligott

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=lois@novonordisk.com  
Date: 2009.02.26 10:48:20 -0500

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**NDA Amendment**



February 25, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated February 11, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the February 11, 2009 request received from John Bishai, FDA Project Manager, for clarification on information regarding surgical pathology reports that had previously been submitted on November 14, 2008.

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5530 created on February 19, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

**Michelle Thompson  
on behalf of Mary  
Ann McElligott**

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Digitally signed by Michelle Thompson on behalf  
of Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=mtho@novonordisk.com  
Date: 2009.02.25 14:08:50 -05'00'

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

## Bishai, John

---

**From:** Bishai, John  
**Sent:** Wednesday, February 18, 2009 1:19 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** NDA 22341 MACE question regarding why estimates change for Custom but not for Broad or Narrow endpoints

Hello Michelle,

While reviewing you're the updated MACE analysis we had the following question:

In your submission from 13 Feb 2009, you provide updated MACE analyses which have added an event of ischemic stroke, which occurred in a patient in an active control arm. On serial page 23 of the submission, in Table 3, we note that (when comparing your new estimates to those from your 21 Jan 2009 submission) the addition of this event changed the point estimates and confidence intervals for the FDA Custom endpoint for Populations A2 and B, but it did not change the point estimates or confidence intervals for the Broad or Narrow SMQ endpoints, which also should have included the term "ischemic stroke". It seems that, since all three endpoint composites included "ischemic stroke", all analyses with pooled comparator or active comparator had the potential for slight changes in point estimates and confidence intervals. Did you include the event of ischemic stroke in your updated analyses for the Broad SMQ and Narrow SMQ endpoints?

If you have any questions, feel free to contact me.

Thanks,  
John

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this page is the manifestation of the electronic signature.**  
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/s/

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John M Bishai  
2/20/2009 07:05:57 AM  
CSO

NDA Amendment



February 20, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated February 18, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the February 18, 2009 request received from John Bishai, FDA Project Manager, for clarification on major adverse cardiovascular events (MACE) analysis that had previously been submitted on February 13, 2009.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5530 created on February 19, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**  
on behalf of Mary  
Ann McElligott

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs, email=mtho@novonordisk.  
com  
Date: 2009.02.20 09:24:49 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

## **Response to FDA Request dated 18 February 2009**

# **Liraglutide**

## **Request and Response**

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## 1 NDA 22-341 (liraglutide) Response to 18 February 2009 Request

The liraglutide diabetes New Drug Application (NDA) (22-341) was submitted on the 23 May 2008. The following questions were received on February 18, 2009 from the Medical Reviewer.

### 1.1 Question (MACE Analysis)

*In your submission from 13 Feb 2009, you provide updated MACE analyses which have added an event of ischemic stroke, which occurred in a patient in an active control arm. On serial page 23 of the submission, in Table 3, we note that (when comparing your new estimates to those from your 21 Jan 2009 submission) the addition of this event changed the point estimates and confidence intervals for the FDA Custom endpoint for Populations A2 and B, but it did not change the point estimates or confidence intervals for the Broad or Narrow SMQ endpoints, which also should have included the term "ischemic stroke". It seems that, since all three endpoint composites included "ischemic stroke", all analyses with pooled comparator or active comparator had the potential for slight changes in point estimates and confidence intervals. Did you include the event of ischemic stroke in your updated analyses for the Broad SMQ and Narrow SMQ endpoints?*

In a second e-mail, the Medical Reviewer also asked:

*I am wondering if the explanation is that "ischemic stroke" was included in the Broad and Narrow SMQ analyses for the Jan 21st submission, but just not for the Custom endpoint in the Jan 21st submission. That would make sense since those were standard queries. If that was the case, that term would only have been added to the Custom endpoint for the 13 Feb submission.*

The answer is correct - the spelling mistake only affected the custom analysis as the SMQs were predefined and therefore the ischemic stroke has been (21<sup>st</sup> Jan) and still is (13<sup>th</sup> Feb) included in the SMQ analysis.



MEMORANDUM

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

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DATE: February 18, 2009

FROM: Sriram Subramaniam, Ph.D.  
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. CTV 2/18/09  
Associate Director - Bioequivalence  
Division of Scientific Investigations

TO: Mary H. Parks, M.D.  
Director, Division of Metabolic and Endocrine  
Products

SUBJECT: Review of EIRs Covering NDA 22-341, Victoza®  
[Liraglutide Injection], Sponsored by Novo Nordisk  
A/S Global Development

At the request of the Division of Metabolic and Endocrine Products (DMEP), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

**Study NN2211-1692:** A randomized, double-blind, single-centre, two-period, cross-over trial in healthy subjects investigating the bioequivalence between the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4)

The clinical and analytical portions of the study were conducted at Clinical Pharmacology Phase I Unit, Lund University Hospital, Lund, Sweden, and \_\_\_\_\_, respectively. In addition, Novo Nordisk, Copenhagen, Denmark was also for the above study. This report is limited to audit of the analytical portion of the study at \_\_\_\_\_ and Novo Nordisk. The report of the clinical portion will be forwarded as a separate report.

Following the inspection at \_\_\_\_\_ Form FDA 483s were issued (1/5-9/09). No Form 483 was issued at Novo Nordisk (1/12-13/09). The evaluation of the significant findings follows:

b(4)

b(4)

Analytical Site: \_\_\_\_\_

b(4)

**a. Failure to demonstrate consistency in accepting the calibration standards. (Item 1, Form 483).**

For example in Run 186, for the LLOQ standard, the mean of the duplicate concentrations\* was used although one of the duplicates was greater than 30% (Exhibit 1). In the same run, for the 132 and 267 pmol/L standards, the mean of the duplicates was not used although both duplicate concentrations were acceptable; instead only one of the duplicates was used to estimate the calibration response. Also, in several runs, one or both of the duplicate standards with inaccurate values were inconsistently accepted or rejected. The firm's SOP lacked explicit criteria for rejection of replicate standards and reporting means. During the inspection, the firm stated that the standard acceptance criteria for the study were that LLOQ standards should be \_\_\_\_\_ of the nominal and the remaining standards should be \_\_\_\_\_ of the nominal. The inspection found that acceptance of calibration standards was not consistent in at least 35% of the total runs (see examples in Table 1). Therefore, the accuracy of the runs, as estimated by the firm, cannot be assured.

b(4)

**b. Failure to demonstrate consistency in accepting Quality Control (QC) values. (Item 2, Form 483)**

In about 16% of the analytical runs (runs 86, 113, 184, 186, 187, 189, 190, 193, and 231), the mean (of duplicates) concentrations of both QCs at the same level were outside the acceptance limits. The firm's run acceptance criterion

\_\_\_\_\_ However, in the above runs, the firm \_\_\_\_\_

b(4)

\_\_\_\_\_ (Exhibits 1 and 2). The objectivity of this assessment is questionable as the error was not documented during sample handling, instead was recorded after sample analysis. Consequently, the accuracy of runs 86, 113, 184 and 231 cannot be assured†, as the runs failed to meet the firm's run acceptance criteria.

**c. Failure to demonstrate acceptable precision for the low QC (about 70 pmol/L). (Item 3, Form 483)**

During the study, study samples were analyzed using two batches of QCs (Runs 85-160 used one batch, and runs 182-287 used another batch). The assay performance of both the batches

\* Each sample (calibrators, QCs and study samples) was analyzed in duplicate and mean of duplicate concentrations reported.

† Please refer to Item a for Runs 186, 187, 189, 190 and 193.

showed imprecision at the low QCs (%CV >  $\frac{1}{2}$ ). Also, cross validation performed by \_\_\_\_\_ during method transfer also showed imprecision at the low QCs. b(4)

- d. Failure to document the loading and checking of \_\_\_\_\_ with specific details to the sample identity with regard to the location in the \_\_\_\_\_, although templates were available. (Item 6, Form 483)** b(4)

There was no independent check to identify the location of samples loaded in the \_\_\_\_\_ for each analytical runs. Although sample list was available for each analytical run, there was no documentation cross referencing the sequence number in the sample list to the wells in the \_\_\_\_\_. The firm stated that they followed the template listed in their SOP for \_\_\_\_\_. Firm should have documentation to verify the location of samples in \_\_\_\_\_ for each analytical run. b(4)

- e. Failure to include QCs for precision and accuracy calculation from runs 205, 218 and 280, although study samples were analyzed in these runs. (Item 4, Form 483)** b(4)
- \_\_\_\_\_ did not include QC data from all valid analytical runs used for study sample analysis for assessing assay performance during the study. QC data from all valid analytical runs should be used to assess in-study assay performance.

- f. Failure to investigate and carry out a root cause analysis for runs 162 - 180 (about 19 runs with approximately 400 samples) that were rejected for "preparation error". (Item 8, Form 483)**
- Runs 162-180 were rejected due to "preparation error". During the inspection, \_\_\_\_\_ stated that a new batch of standards was used for these runs, and the observed concentrations of the calibrators were often inaccurate. Therefore, \_\_\_\_\_ rejected the runs, and labeled them as "preparation error". Although source data for these runs indicated that the runs were rightly rejected, "preparation error" was not discernable. \_\_\_\_\_ should have conducted a root cause analysis to identify the reason for the failure of the 19 runs. b(4)

- g. No available data during the assay performance to show the presence, the interference and extent of elimination of endogenous GLP1. (Item 9, Form 483)**
- Prior to analysis, samples were incubated at \_\_\_\_\_. During cross validation, \_\_\_\_\_ analyzed \_\_\_\_\_ (with endogenous GLP1 alone), and observed mean concentrations b(4)

of ~500 pmol/L following incubation at \_\_\_\_\_. The sponsor stated that liraglutide immunoassay also detects endogenous GLP1 as the primary antibody binding sites are the same for both compounds. Further, according to the sponsor, since the nominal endogenous GLP1 concentration of the \_\_\_\_\_ was 10,000 pmol/L, the observed \_\_\_\_\_ concentrations ( \_\_\_\_\_ pmol/L) after \_\_\_\_\_ suggest degradation of \_\_\_\_\_ of endogenous GLP1. However, \_\_\_\_\_ did not quantify endogenous GLP1 concentrations in subject samples. However, during the inspection at Novo Nordisk this issue was clarified (see below).

b(4)

In addition, the inspection also found that \_\_\_\_\_ did not use independent stocks for standard and QC preparations, and lacked accountability for worksheets used by analysts. These findings are not likely to impact the current study. Nonetheless, the firm needs to correct these objectionable practices for future studies.

b(4)

**Sponsor Site: Novo Nordisk, Copenhagen, Denmark**

The sponsor showed data to indicate that the circulating endogenous GLP1 in human plasma was between 30-50 pmol/L. Therefore, extrapolation of the \_\_\_\_\_ data at \_\_\_\_\_ would suggest that negligible endogenous GLP1 should remain in plasma samples following \_\_\_\_\_. Also, sponsor's measurement of liraglutide in presence of 100 pmol/L endogenous GLP1, both in the presence or absence of \_\_\_\_\_ demonstrated that the accuracy of liraglutide measurement was not affected by physiological concentrations of endogenous GLP1.

b(4)

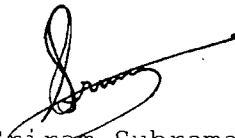
**Conclusions**

Based on the above findings, DSI concludes the following:

1. \_\_\_\_\_ (analytical facility) should reestimate calibration curves for all analytical runs in a consistent manner using explicit and objective criteria for calibration standard acceptance. Only those subject concentrations from analytical runs that meet the QC acceptance criteria should be accepted for bioequivalence assessment and bioequivalence be reevaluated (Item a).
2. The subject concentration data from analytical runs 86, 113, 184 and 231 are not acceptable as the accuracy of the analytical runs is not assured (Item b).

b(4)

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Sriram Subramaniam, Ph.D.

Table 1

Analytical runs with inconsistent standard acceptance.

Runs	Comments
90	
97	
99	
106	
121	
125	
126	
128	
147	
148	
186	
187	
189	
190	
191	
192	
193	
206	
212	

b(4)



10 Page(s) Withheld

√ Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)



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this page is the manifestation of the electronic signature.**  
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/s/

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Sriram Subramaniam  
2/18/2009 03:23:54 PM  
PHARMACOLOGIST

This report includes audit findings from analytical portion of  
the BE study. Clinical portion will be forwarded  
in a separate report.

NDA Amendment



February 13, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated January 30, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the January 30, 2009 request received from John Bishai, FDA Project Manager, for clarification on the data regarding major adverse cardiovascular events (MACE) that had previously been submitted on January 21, 2009 (Version 1).

At this time, Novo Nordisk is providing the requested information as an Amendment to NDA 22-341. Additionally, we are providing a revised MACE analysis (Version 2) which incorporates this updated information.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5523 created on February 11, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.  
**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.02.13 13:19:38 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



February 13, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza<sup>®</sup> [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated February 9, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the February 9, 2009 request received from John Bishai, FDA Project Manager for definitions of diabetes complications.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5523 created on February 11, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.02.13 08:54:46 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



February 11, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated January 8, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the January 8, 2009 CMC Discipline Review Letter.

At this time, Novo Nordisk is also providing the responses to the deficiencies cited in the letter as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 6 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5521 created on February 9, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.  
**Michelle Thompson on  
behalf of Mary Ann  
McElligott**

Digitally signed by Michelle Thompson on behalf of  
Mary Ann McElligott  
DN: cn=Michelle Thompson on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2009.02.11 15:11:22 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Bishai, John**

**From:** Bishai, John **Sent:** Mon 2/2/2009 3:44 PM  
**To:** MTHO (Michelle Thompson)  
**Cc:**  
**Subject:** Response to your Chemistry inquiry  
**Attachments:**

Hello Michelle,

After discussing your question, the chemistry had the following comment:

There is insufficient information in the your response, dated August 25, 2008, to adequately evaluate your proposal to add a test of total dose of assembled drug product as a drug product specification rather than an in-process control of the filling volume. The proposed total dose test should be adequate to ensure the successful delivery of a) 15 doses of 1.2 mg liraglutide, and b) 10 doses of 1.8 mg liraglutide. The test should include realistic in-use conditions such as \_\_\_\_\_ of the injector. In order to determine if your proposal is adequate, a description of the test should be provided, including details of realistic in-use conditions

b(4)

If you have any questions, please let me know.

Thanks,  
John

---

**From:** MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]  
**Sent:** Fri 1/30/2009 5:34 PM  
**To:** Bishai, John  
**Subject:** RE: A couple of questions regarding MACE events

Hi John,

I have forwarded the questions to my colleagues in HQ and am hoping to have a response for you very soon. We are working on a response to the CMC Review letter and have the following clarifying question to the reviewer:

In our response to the CMC reviewer request C, in the day-74 Filing communication letter (Novo Nordisk response of August 25, 2008), we proposed to add a test of total dose of assembled drug product as a drug product specification test. Can you confirm your agreement with our proposal to add this test to the drug product specification?

Please don't hesitate to contact me if you have any questions. Thanks.

Michelle

---

**From:** Bishai, John [mailto:John.Bishai@fda.hhs.gov]  
**Sent:** Friday, January 30, 2009 9:07 AM  
**To:** MTHO (Michelle Thompson)  
**Cc:** Derr, Janice; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** A couple of questions regarding MACE events

Hello Michelle,

First, I wanted to thank you for expedited response to our MACE request. After reviewing the data, we have the following questions:

1. In your submission from 21 Jan 2009, in Appendix A, you provided listings of MACE events in two tables.

We note that in the columns entitled "Time on study at time of event", some of the events do not have a number in that cell. Is this because the data are not available, or the events occurred prerandomization, or is there another reason?

2. On page 10 of that listing, Patient 770002 was listed as having an ischemic stroke. The listing states that the event was not included in the Custom MACE, but an event of ischemic stroke should have been included per the FDA request. Is this a typographical error, or was the event actually not included when you performed your analyses?

Thanks,  
John

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/s/

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John M Bishai  
2/3/2009 09:18:58 AM  
CSO

NDA Amendment



January 21, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated January 11, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the January 11, 2009 request received from John Bishai, FDA Project Manager for data regarding major adverse cardiovascular events (MACE).

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 6 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5500 created on January 20, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary  
Ann McElligott**

Digitally signed by Lois Kotkoskie on behalf  
of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary  
Ann McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.01.21 11:49:54 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



NDA Amendment



January 16, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated December 16, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the December 16, 2008 request received from John Bishai, FDA Project Manager for a table of serious adverse events for all completed trials.

The requested information is being provided as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5495 created on January 15, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of  
Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann  
McElligott, c=US, o=Novo Nordisk Inc,  
ou=Regulatory Affairs,  
email=loko@novonordisk.com  
Date: 2009.01.16 10:40:49 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

# Memo

**To:** Michelle Thompson of Novo Nordisk

**From:** John Bishai

**CC:**

**Date:** January 16, 2009

**Re:** Phone call to discuss the Agenda for the upcoming Advisory Committee meeting for NDA 22-341.

---

On Thursday, January 15, 2009, Drs. Mary Parks and John Bishai called Novo Nordisk to discuss the agenda for the upcoming Advisory Committee (AC) for NDA 22-341. During the phone call, Dr. Mary Parks repeatedly stated that the AC meeting will primarily focus on the Cardiac Risk/Benefit Analysis and the nonclinical finding of c-cell hyperplasia in rodents.

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/s/

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John M Bishai  
1/16/2009 02:23:51 PM  
CSO

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Wednesday, January 14, 2009 9:20 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** RE: NDA 22-341 Clarification on MACE request dated 1/11/09

Hello Michelle,

After discussing the issues with the team, we feel that the suggested analysis period up until the the 120 day update is satisfactory. We also feel that a recoding of the data is not necessary. However, in the event that a recoding is necessary, we ask that you provide a listing of all recoded events along with the original coding. We would also like to take this time to remind you to define the analysis populations as detailed in points I.A. and I.B. of our letter.

If you have any questions, please feel free to contact me.

Thanks,  
John

---

**From:** MTHO (Michelle Thompson) [mailto:mtho@novonordisk.com]  
**Sent:** Wednesday, January 14, 2009 1:24 PM  
**To:** Bishai, John  
**Subject:** NDA 22-341 Clarification on MACE request dated 1/11/09

Hi John,

As discussed we will conduct the analysis on all data included in the 120-day update. We need confirmation on the following:

Adverse events reported in the original NDA were coded using MeDRA version 10.1, new adverse events reported in the 120-day safety update were coded using MeDRA version 11.0. For the requested analysis, there will be no changes in MeDRA coding i.e recoding to version 10.1.

Please confirm that this is acceptable. Don't hesitate to contact me should you have any questions.

Michelle

---

**Michelle Thompson**  
Director Regulatory Affairs (SMART)  
Clinical, Medical, Regulatory

Novo Nordisk Inc.  
100 College Road West  
Princeton, New Jersey 08540  
USA  
(609)987-5972 (direct)  
(609)933-5079 (mobile)  
MTHO@novonordisk.com

1/14/2009

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 unauthorised 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.

1/14/2009

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/s/

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John M Bishai  
1/14/2009 09:30:35 PM  
CSO

**NDA Amendment**



January 14, 2009

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated January 13, 2009**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the January 13, 2009 request received from John Bishai, FDA Project Manager for datasets for study NN2211-1571.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5493 created on January 12, 2009. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lois Kotkoskie on  
behalf of Mary Ann  
McElligott**

Digitally signed by Lois Kotkoskie on behalf of Mary Ann McElligott  
DN: cn=Lois Kotkoskie on behalf of Mary Ann McElligott, c=US, o=Novo Nordisk Inc, ou=Regulatory Affairs, email=loko@novonordisk.com  
Date: 2009.01.14 12:39:08 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



NDA 22-341

**INFORMATION REQUEST LETTER**

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 May 23, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

In anticipation of the upcoming Advisory Committee meeting for your product, we request that you submit for our review the following data regarding major adverse cardiovascular events (MACE).

Submit the requested data no later than January 21, 2009, to ensure that there is sufficient time for review.

Please provide information and analyses regarding MACE events as follows:

I. Analysis population(s):

A. The main analysis population should include the randomized, double-blind, controlled periods for all completed Phase 2 and Phase 3 trials of your product.

B. An additional analysis population should include the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of your product. That is, include unblinded periods if they remain controlled, and include controlled data past the primary HbA1c efficacy measurement, if applicable. Do not include uncontrolled extension periods.

II. Endpoints: Use the following two endpoints, which will be referred to hereafter as "SMQ MACE" and "Custom MACE". We acknowledge that there may be many opinions about what precise terms should be included in these endpoints, but these are the terms we want you to use. For nonfatal events, use MedDRA Preferred Terms as they were originally assigned in your NDA submission. Do not use post hoc adjudication for nonfatal events. Adjudication of cardiovascular deaths is acceptable. Do not add or subtract Preferred Terms from either endpoint. If you wish to provide separate analyses with independent external post hoc



adjudication of nonfatal events from the specified endpoints, you may do so, but you must submit the analyses with unadjudicated Preferred Terms for nonfatal events as requested.

“SMQ MACE”: Use a composite endpoint of cardiovascular death, and all Preferred Terms in the Standardised MedDRA Queries for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents”.

“Custom MACE”: Use a composite endpoint of cardiovascular death and the following MedDRA Preferred Terms:

- Acute myocardial infarction
- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Coronary artery thrombosis
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Postprocedural stroke
- Silent myocardial infarction
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

### III. Types of Analyses

#### A. Listing

List all events (including those from uncontrolled portions of the trials) from both the “SMQ MACE” and the “Custom MACE” endpoints, including both the first event observed and any subsequent events observed. The listing should be sorted by treatment group and patient ID. For patients with multiple events, the events should be listed in order of occurrence. The events should be defined by MedDRA Preferred Terms. A proposed format for this listing is shown below:

Table 1 (example) Listing of MACE events sorted by treatment group and type of event for all studies

Pt ID	Study	Treatment	MedDRA Preferred Term	Date of event	Time on study at time of event	In the main analysis population?	Serious event?	SMQ MACE?	Custom MACE?

#### B. Summaries

1. Summary of the incidence of SMQ MACE and Custom MACE events in the main analysis population and in the additional analysis populations by dose of the study drug. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 2 (example) Incidence of SMQ MACE events in the main analysis population, by dose of study drug

	Dose 1	Dose 2	Dose 3	All Doses	Placebo Comparator	Active Comparator
Pooled	x/X (y%)					
Study 1						
Study 2						
Study 3						
Study 4						

x= number of events for that group

X=total number of randomized patients in the safety database for that group

y=x/X times 100

2. Summaries of the incidence of SMQ MACE events and Custom MACE events in the main analysis population and the additional analysis population, combined across doses of the study drug in separate tables. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE events and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 3 (example) Incidence of SMQ MACE events in the main analysis population, combined across doses of study drug, reported separately by study

Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (events/N)	Incidence ratio, 95% CI	Incidence difference, 95% CI	Incidence rate (events/Pt -yrs)	Incidence rate ratio, 95% CI	Incidence rate difference, 95% CI
Study 1	Study Drug									
	Active Comparator									
	Placebo Comparator									
Study 2	Study Drug									
	Active Comparator									
	Placebo Comparator									
etc	etc									
etc	etc									
Overall results stratified by study										

### C. Analyses

For SMQ MACE and custom MACE, analyze both the incidence (events/N) and the incidence rate (events/patient-year) using the analysis populations described under I. A. and B. of this document. If the set of Phase 2 and 3 studies has more than one type of comparator group, we recommend making three comparisons: a) the study drug compared to the placebo; b) the study drug compared to the active comparator; and c) the study drug compared to the placebo and the active comparator groups combined. Analysis c) is the analysis that should be presented in the last line of Table 3 and the Forest plots discussed in Section D.

The analyses should be stratified by study and we recommend that a stratified exact method be included as one of the analyses. However, we acknowledge that multiple studies may have 0

MACE events in one or more groups and that pooling studies for an unstratified analysis may be a reasonable alternative.

#### D. Forest Plots

For SMQ MACE and custom MACE, provide a forest plot depicting the incidence ratio results from the individual studies and the results from the overall stratified analysis for the primary analysis population described in I. A.

#### E. Electronic Data Files

Please provide a dataset with a single observation for each patient which includes the following:

- Study identifier
- Unique patient identifier
- Demographic data
- Date of randomization
- Treatment group
- Date of completion/rescue/discontinuation of the randomized, controlled, double-blind period of the study
- Exposure time in the randomized, controlled, double-blind period of the study
- Participated in extension study (Yes/No)
- For each of the composite endpoints ("SMQ MACE" and "Custom MACE"), include the following set of variables:
  - a) Duration of time from randomization to date of first event or censoring
  - b) Indicator for whether or not the event took place during the double blind period
  - c) Censoring variable
  - d) Date of event or censoring
- MedDRA Preferred Term for "SMQ MACE"
- MedDRA Preferred Term for "Custom MACE"

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at 301-796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Hylton Joffe  
1/11/2009 01:28:56 PM  
Hylton Joffe for Mary Parks



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-341

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

We also refer to your December 24, 2008, correspondence, received on December 24, 2008, requesting a meeting to discuss a proposal for a post-approval cardiovascular outcome study and your proposed risk management plan. We have considered your request and concluded that the meeting is premature. The Division is in the process of preparing a new information request, expected to issue this month, regarding liraglutide cardiovascular data. We will first need to review your response to this information request before discussing the type and scope of a post-approval cardiovascular outcome study. With regard to the risk management plan, we have not completed all necessary components of the safety review to permit a sufficient appraisal of your proposal.

If you have any questions, call me at (301) 796-1311.

Sincerely,  
*{See appended electronic signature page}*

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

-----  
John M Bishai  
1/9/2009 03:46:38 PM

**REQUEST FOR CONSULTATION**

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
1/8/09

IND NO.

NDA NO.  
22-341

TYPE OF DOCUMENT  
Original IND

DATE OF DOCUMENT  
December 19, 2008

NAME OF DRUG  
Victoza (Liraglutide  
Injection)

PRIORITY CONSIDERATION  
Priority

CLASSIFICATION OF DRUG  
Treatment of Type II  
diabetes

DESIRED COMPLETION DATE  
February 18, 2009

NAME OF FIRM: Novo Nordisk

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

**II. BIOMETRICS**

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

**III. BIOPHARMACEUTICS**

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

**IV. DRUG SAFETY**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This a request for a Draft Carton and Container Label Review. The document can be found in the EDR (see link below). Please note this submission also includes an \_\_\_\_\_ 1.8 mg pen \_\_\_\_\_ : However the scale drum is marked to deliver all treatment doses. **b(4)**

Direct link to edr: \\CDSESUB1\EVSPROD\NDA022341\022341.ENX

SIGNATURE OF REQUESTOR  
JB

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND



PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

-----  
John M Bishai  
1/8/2009 02:01:06 PM



8. Note: A shelf life of 18 months will be granted for the drug substance when stored at  $-18^{\circ}\text{C} \pm 2^{\circ}\text{C}$ /ambient % RH or lower temperatures. This is based on acceptable long term stability results from real-time studies obtained for the drug substance from Campaign ✓ since the final step (Step ✓), in the manufacture of liraglutide drug substance has changed significantly from earlier campaigns.

b(4)

Drug Product

9. Provide a thorough explanation of the factors involved for making the significant change described in Section 3.2.P.2.2, page 10: \_\_\_\_\_  
\_\_\_\_\_
10. Fully describe the analytical method, Thioflavine T (ThT), used to assess the physical stability (tendency to \_\_\_\_\_) of the API in the drug product. Also, provide evidence showing how increased \_\_\_\_\_ tendency adversely impacts upon the quality attributes of the drug product.
11. Provide the protocols for determining total extractables of the rubber stopper and disc laminate used for liraglutide 6.0 mg/mL. Also, provide the identities of all extractables found during the extractables studies.
12. It is unclear if compatibility, extractables and leachables studies were conducted using \_\_\_\_\_, as described in Description of Manufacturing Process and Process Controls (3.2.P.3.3). If not, provide justification for conducting these studies on non-siliconized rubber.
13. Provide descriptions of the processes employed for \_\_\_\_\_ the a) 3 mL cartridges, and b) rubber plunger. Also, provide a certificate of analysis or specifications for the medical grade \_\_\_\_\_ processes.
14. Provide justification for using a  $C_{pk}$  value of \_\_\_\_\_ for determining the specification limits of liraglutide content in the drug product when a  $C_{pk}$  value of \_\_\_\_\_ was used in the justification of the drug substance specifications. (In Section 3.2.S.4.5, page 7, Justification of Specification for the Drug Substance: "Usually company standard is to require that  $C_{pk}$  is greater than 1.33.")
15. The URL for liraglutide content in the drug product specifications should not exceed the calculated value, i.e., 103.1% (rather than the proposed URL of \_\_\_\_\_ %).
16. Revise the release and shelf life limits of the product related impurities of the drug product specifications (Sum of Liraglutide Related Impurities, Other \_\_\_\_\_ Liraglutide Related Impurities, Liraglutide related Impurities A, Liraglutide Related Impurities B, Liraglutide Related Impurities C, Other \_\_\_\_\_ Liraglutide Related Impurities and High Molecular Weight Proteins) based on revisions to the corresponding limits in the drug substance specifications (see comment #5 above).

b(4)

b(4)

b(4)

b(4)

b(4)

b(4)

17.

b(4)

18. Note: The three drug product pilot batches (SQ50423, SQ50447, SQ50549) are considered to be the primary stability batches, found acceptable by FDA at the pre-NDA stage. These batches, produced in Campaign 6, will be considered for assessing real time stability (and not supportive batches produced in Campaigns 4B and 5A). The formulation, the drug substance and drug product manufacturing process for the three primary drug product batches tested in this real time stability studies (and subsequent in-use study) are identical to the ones that will be used for the marketed product. Stability data for these batches through 18 months of real time stability testing show that the liraglutide 6.0 mg/mL drug product remains within the revised shelf life specification limits. According to ICH Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products), "(drug) product expiration dating should be based upon the actual date submitted in support of the application." Therefore, your proposal of a / month shelf life period is not warranted. An expiry of 18 months at 2 – 8°C plus 32 days at 28 – 32°C is granted for the drug product.

b(4)

19. Continue to monitor specific bioactivity of the drug product as part of the postapproval stability protocol as it was included in the original stability protocol of the three primary, supportive and process validation batches.

20. Submit data to support the proposed additional assembly site of liraglutide \_\_\_\_\_ as a Changes Being Effected (CBE-0) postapproval supplement rather than submitted in an annual report. Also, provide the complete address of the proposed additional manufacturing site for assembly of liraglutide \_\_\_\_\_ located in \_\_\_\_\_

b(4)

21. Submit data to support the addition of a new manufacturing site of the drug product as a Prior Approval Supplement (PAS) rather than in an annual report. This will allow FDA to determine the CGMP status of the new manufacturing site for the intended purpose of manufacturing the drug product, liraglutide 6 mg/mL, 3 mL cartridge. Based on several factors, such as, the drug substance being a new molecular entity, the drug product is \_\_\_\_\_ processed and the dosage form a solution for injection, the proposed addition of a manufacturing site for the drug product is identified as having a substantial potential to adversely affect the quality, purity or potency of the drug product.

b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call John Bishai Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

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John M Bishai  
1/8/2009 12:27:29 PM

NDA Amendment



December 23, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – Response to FDA request for information dated December 17, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the December 17, 2008 request received from John Bishai, FDA Project Manager.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 6 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5472 created on December 22, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle**  
**Thompson**

Digitally signed by Michelle Thompson  
DN: cn=Michelle Thompson, c=US,  
o=Novo Nordisk Inc., ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2008.12.23 15:39:01 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



## **Response to FDA Request dated 17 December 2008**

### **Liraglutide**

### **Requests and Response**

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## List of Abbreviations and Definition of Terms

NDA	New Drug Application
PK	Pharmacokinetic(s)

## 1 Clinical Pharmacology Requests

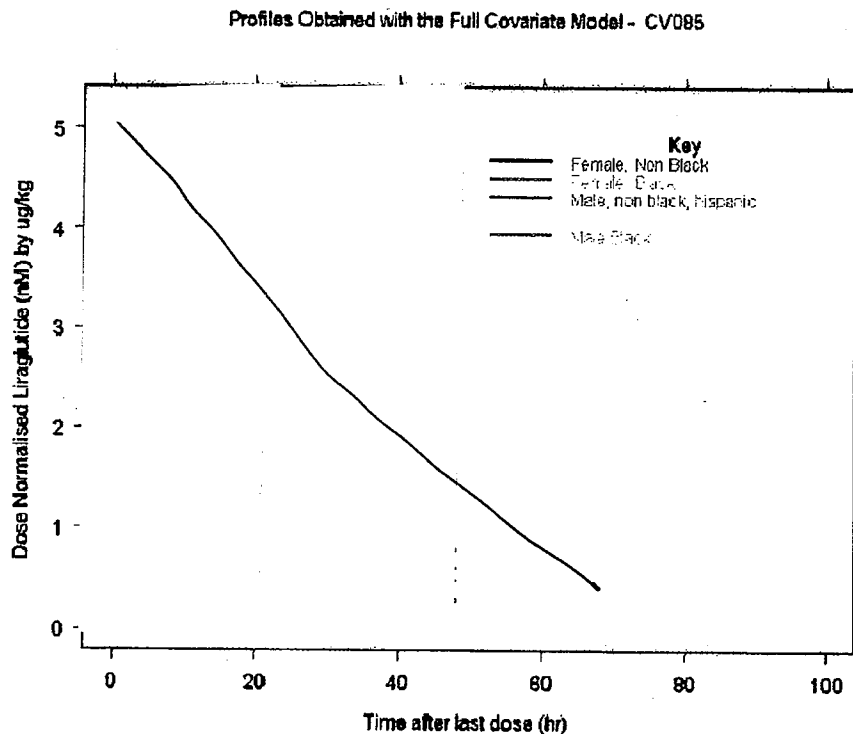
The liraglutide diabetes New Drug Application (NDA) (22 341) was submitted on the 23 May 2008. After reviewing an information response submitted to the FDA on 3 October 2008, the FDA Clinical Pharmacology team had posed the following questions on 17 December 2008.

### 1.1 Question 1

We have found an inconsistency in your dataset, entitled finaldat.xpt, which was submitted on 10/03/2008. While reproducing the observed concentration-time profile after the last dose, we noted that when utilizing the finaldat.xpt data set, the graph [Figure 2. (A)] yielded was different from your Figure 1 with regards to the time scale. It seems that "TIME" and "TALD" columns in the dataset (finaldat.xpt) appear to have similar values [Figure 2.(B)]. *If applicable, please submit a revised data set as soon as possible.*

Figure 1.

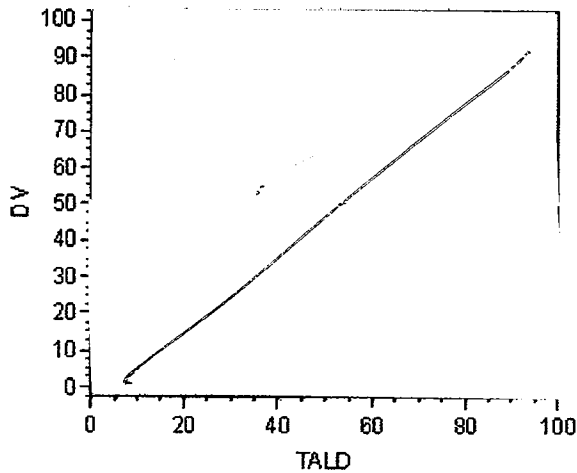
#### A) Linear Scale



b(4)

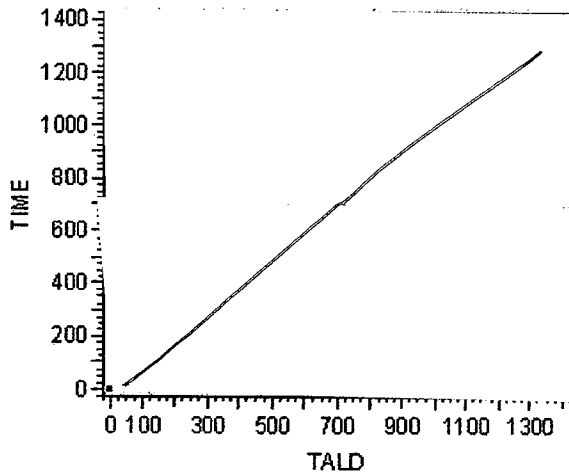
Figure 2.

(A)



b(4)

(B)



### Response

We acknowledge there was an error in the dataset final.xpt delivered on 3 October 2008 and a revised dataset will be submitted. The pharmacokinetic (PK) modelling described in the Biomodelling report was not affected by the erroneous values in the TALD-variable.

Novo Nordisk has identified another error in the Biomodelling report, version 1. Thus an update of the report is enclosed and contains an explanation of the error and a correction of the analysis. The

revised dataset accompanying the updated Biomodelling report, includes the correction of the TALD variable.

## 1.2 Question 2

Based on the concentration versus time-after-last-dose plots, it is apparent that sampling times are greater than 24 hours. Please explain why sampling times exceeded 24 hours considering the recommended dosing regime is once-a-day. In addition, we ask that you provide the Actual Dosing, Sampling Date, and Time information in SAS format.

### Response

In general, although the planned dosing interval was 24 hours, a number of observations had higher TALD values than 24 hours; in total 1289 observations. Of these; 1268 observations were taken between 24 and 40 h following last dose with the majority of these (1173) within 28 hours post last dose time. This was due to a number of factors such as delaying dosing times due to subjects awaiting blood sample being drawn at the day of visit prior to taking their morning dose or missing doses.

There were 21 observations later than 40 hours out of 2970 included observations in total. For all observations with TALD>40h, subjects had recorded the time of the previous two doses at two or more days prior to the visit. This is apparently due to subjects faithfully recording to have missed one or more scheduled doses. In most cases (16 values in 16 subjects), one dose seems to have been missed. This result in a TALD close to 48h if the subject missed a dose in the morning of the day before the visit and had not (yet) dosed himself on the morning of the visit day. In the remaining five cases (TALD 72-100h), two or three doses appear to have been missed and this is consistent with the relatively low plasma exposure found in these samples, see Figure 1.

In 20 cases (in 19 subjects), subjects completed additional visits after the visit with a TALD>40h, or this visit was visit 13. Discontinuation of treatment prior to dropout is therefore not a likely explanation for the long TALD in most subjects concerned. Most probably, the 21 PK observations with TALD >40h, out of 2970 PK observations in this analysis, are due to noncompliance to the once-daily treatment regimen.

The revised dataset mentioned in Question 1 also includes the requested parameters (Actual Dosing, Sampling Date, and Time information).

## REQUEST FOR TYPE A MEETING



December 24, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
Request for Type A Meeting**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the 4-month Safety Update submitted on September 23, 2008.

At this time, Novo Nordisk is requesting a Type A meeting with the Agency. The primary purpose of this meeting is to obtain feedback and reach agreement with the Division on a proposal for a post-approval Cardiovascular Outcome Study. Secondly, we wish to further discuss the adequacy of the Risk Management Plan with the Division. The required information (including a draft list of questions and draft study synopsis) to support this meeting request is provided. More detailed documentation will be provided prior to the agreed upon meeting date.

We propose the dates of January 27, 28, 29, 2009 (afternoon preferable) for the meeting. Representation from Statistics and Clinical is requested. Approximately eight to ten participants from Novo Nordisk representing Statistics, Clinical Development, Project Management and Regulatory Affairs will attend the meeting. Additional participants may attend based on the FDA attendees or issues raised after the review of the pre-meeting package. Please provide a list of FDA attendees when available.

This submission is being provided electronically (approximately 4 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5472 created on December 22, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

**Michelle  
Thompson**

Digitally signed by Michelle Thompson  
DN: cn=Michelle Thompson, c=US,  
o=Novo Nordisk Inc., ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2008.12.24 10:48:48 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
[www.novonordisk-us.com](http://www.novonordisk-us.com)



General Correspondence



December 23, 2008

Oumou Barry, Associate Director  
Division of Field Investigations (HFC-130)  
International Operations Branch  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
Confirmation of GCP Inspection**

Dear Ms. Barry:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the December 12, 2008 letter from you announcing and requesting confirmation of the routine bioequivalence monitoring (BIMO) -Bioequivalence inspection to be conducted from January 26 through January 30, 2009 at:

Clinical Pharmacology Phase I Unit,  
Lund University Hospital  
SE-221 85 Lund  
Lund, Sweden

Novo Nordisk hereby confirms the following:

- dates of inspection
- the inspection initiation meeting at 8:00 am with FDA Investigators Thomas Gordon and Lisa Capron on the January 26, 2009
- a copying system will be available for the use of the investigators during the duration of the inspection, and
- documents for review will be available and easily accessible to the investigators during the inspection.

This submission is being provided electronically (approximately 1 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5471 created on December 21, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle  
Thompson**

Digitally signed by Michelle Thompson  
DN: cn=Michelle Thompson, c=US,  
o=Novo Nordisk Inc., ou=Regulatory  
Affairs, email=mtho@novonordisk.  
com  
Date: 2008.12.23 13:52:51 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

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NDA Amendment



December 19, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Update of Stability Information**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the pre-NDA meeting of February 5, 2008 where the Division accepted our proposal to update the file with drug substance and drug product stability information.

Therefore, we are providing the following updated drug substance stability information:

- Supportive Stability Data for Liraglutide Drug Substance from Pilot Scale (
- Primary Stability Data for Liraglutide Drug Substance from Pilot Scale (
- Stability Data for Liraglutide Drug Substance from Manufacturing Scale (
- Stability for Intermediates in the Drug Substance Manufacturing Process

These reports are located in Module 3.2.S.7.3

We are also providing the following updated drug product stability information:

- Supportive Stability Data for Liraglutide 6.0 mg/ml, 3 ml Cartridge (
- Primary Stability Data for Liraglutide 6.0 mg/ml, 3 ml Cartridge (
- PV Stability Data for Liraglutide 6.0 mg/ml, 3 ml Cartridge (
- Stability Data for One 1000 L Batch of Liraglutide 6.0 mg/ml, 3 ml Cartridge (
- Primary In-use Stability Data for Liraglutide 6.0 mg/ml, 3 ml Cartridge (

These reports are located Module 3.2.P.8.3.

The data in these reports support a drug substance shelf life of / months at -18°C and a drug product shelf life of / months at 2-8°C and demonstrate that all tested parameters are within specification.

b(4)

Additionally, we are including with this submission an alternate device configuration. During the EU regulatory review, EMEA requested that Novo Nordisk make a pen available that would allow patients to inject all applied for doses (0.6, 1.2, 1.8 mg). In response to this request from EMEA as well as a company desire to have global presentations of the drug product, this alternate pen configuration is now being submitted for regulatory approval. These presentations this will allow physicians flexibility in individualizing patient treatment.

The alternate device is identical to \_\_\_\_\_ and all the pens share the same working principle. However the scale drum is marked to deliver all treatment doses. Supportive documentation for this pen configuration is provided in Module 3.2.P Drug Product (Liraglutide 1.2/1.8 pen), and all other information is already included in the current NDA. These documents are consistent with what has been previously submitted to support the existing presentations. We are also providing revised labeling to reflect the addition of this configuration. The draft labeling is the same as the previously submitted labeling with the additional minor pen configuration included.

b(4)

This submission is being provided electronically (approximately 11 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5467 created on December 17, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle Thompson**

Digitally signed by Michelle Thompson  
DN: cn=Michelle Thompson, c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs, email=mtho@novonordisk.com  
Date: 2008.12.19 14:11:54 -0500

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Tuesday, December 16, 2008 11:02 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** Aljuburi, Lina  
**Subject:** Info request for Victoza

**Attachments:** n22341 Sample Table Shell for Submission of All Adverse Events for Victoza.doc

Hello Michelle,

From searching the Victoza NDA submission and from reading your description of analysis sets on page 29 of Module 2.7.4 (Summary of Clinical Safety), it appears that you did not submit a table of all adverse events (by MedDRA System Organ Class and Preferred Term) by dose group from the "all completed trials safety analysis set". We note a table of serious adverse events, but not of all adverse events. If you did submit a table of all adverse events, please specify the location of the table. If not, please submit one. We are attaching a sample table shell.

Regards,  
John



n22341 Sample  
Table Shell for ...

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

-----  
John M Bishai  
12/16/2008 03:41:28 PM  
CSO

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Wednesday, December 17, 2008 2:54 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** Aljuburi, Lina  
**Subject:** Clarification of data submitted to NDA 22-341

**Attachments:** Picture (Enhanced Metafile); Picture (Enhanced Metafile); Picture (Enhanced Metafile)

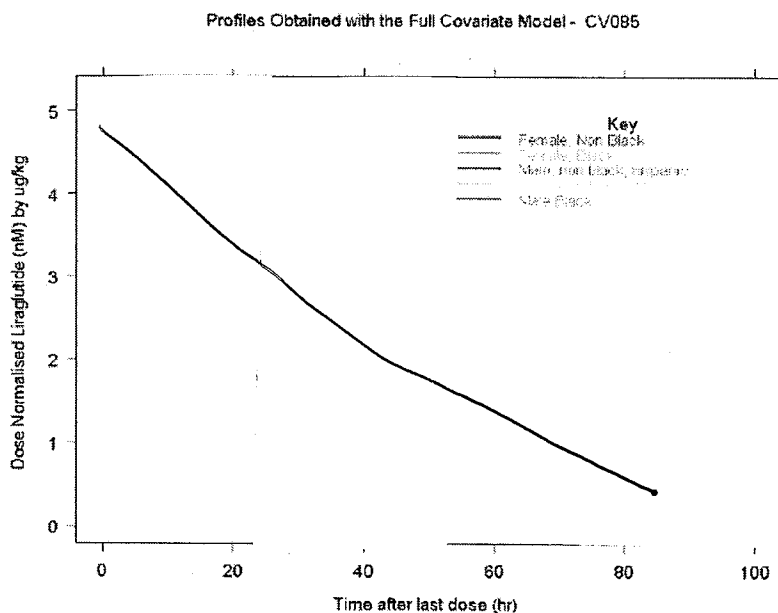
Hello Michelle,

While reviewing your application the Clinical Pharmacology team had the following questions/concerns:

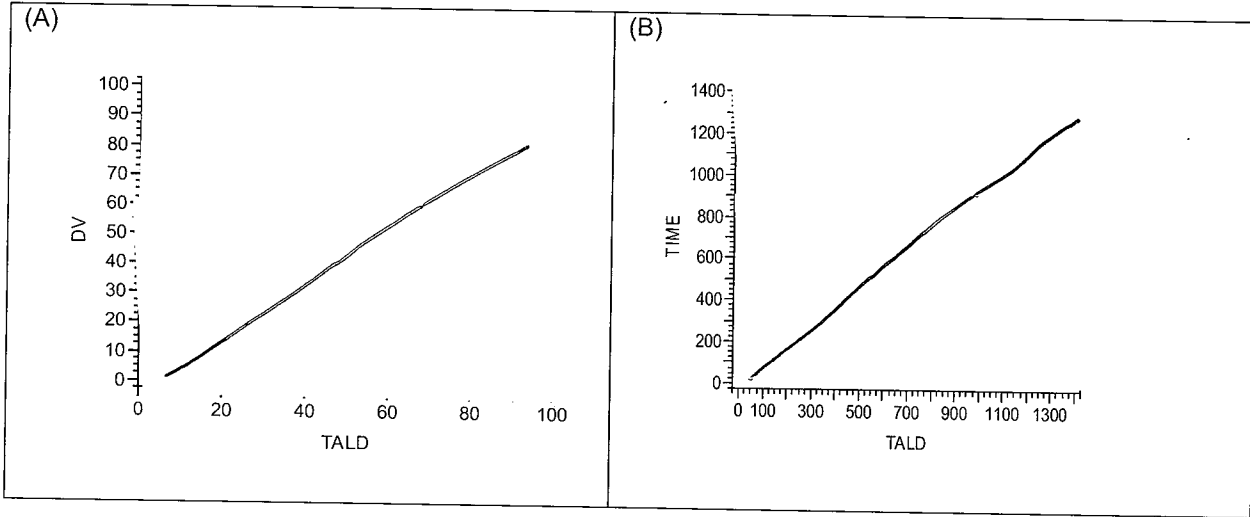
**Question 1:** We have found an inconsistency in your dataset, entitled finaldat.xpt, which was submitted on 10/03/2008. While reproducing the observed concentration-time profile after the last dose, we noted that when utilizing the finaldat.xpt data set, the graph [Figure 2. (A)] yielded was different from your Figure 1 with regards to the time scale. It seems that "TIME" and "TALD" columns in the dataset (finaldat.xpt) appear to have similar values [Figure 2.(B)]. *If applicable, please submit a revised data set as soon as possible.*

**Figure 1.**

A) Linear Scale



**Figure 2.**



b(4)

**Question 2:** Based on the concentration versus time-after-last-dose plots, it is apparent that sampling times are greater than 24 hours. Please explain why sampling times exceeded 24 hrs considering the recommended dosing regime is once-a-day. In addition, we ask that you provide the Actual Dosing, Sampling Date, and Time information in SAS format.



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this page is the manifestation of the electronic signature.**  
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/s/

-----  
John M Bishai  
12/17/2008 02:58:12 PM  
CSO

NDA Amendment



November 14, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated October 27, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the October 27, 2008 request received from John Bishai, FDA Project Manager, to provide entire surgical pathology reports for all cases of thyroid cancer that have occurred in any development program for liraglutide.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 37 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5430 created on November 10, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US,  
o=Novo Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.11.14 12:48:28 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**NDA Amendment**



November 06, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated October 27, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the October 27, 2008 request received from John Bishai, FDA Project Manager, to provide tabular summaries of Major Adverse Cardiovascular Events (MACE) incidence in Phase 2 and 3 studies.

At this time, Novo Nordisk is also providing the requested information as an Amendment to NDA 22-341.

This submission is being provided electronically (approximately 1 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5425 created on November 05, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle  
Thompson**  
Digitally signed by Michelle  
Thompson  
DN: cn=Michelle Thompson, c=US,  
o=Novo Nordisk Inc., ou=Regulatory  
Affairs, email=mtho@novonordisk.  
com  
Date: 2008.11.06 14:23:50 -05'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



October 14, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated October 10, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the October 10, 2008 request received from Karen Mahoney, FDA Medical Reviewer, to provide clarifications regarding the re-analyses of the Major Adverse Cardiovascular Events (MACE).

The responses to the questions were submitted to Dr. Mahoney via email on October 13, 2008. At this time, Novo Nordisk is also providing the requested information as an Amendment to the NDA 22-341.

This submission is being provided electronically (approximately 1 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5401 created on October 08, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

**Sandra C. Cottrell**,  
Ph.D. on behalf of  
Mary Ann  
McElligott, Ph.D.

Digitally signed by Sandra C. Cottrell, Ph.D., on behalf of Mary Ann McElligott, Ph.D.  
DN: cn=Sandra C. Cottrell, Ph.D., on behalf of Mary Ann McElligott, Ph.D.,  
c=US, o=Novo Nordisk Inc.,  
ou=Regulatory Affairs,  
email=scott@novonordisk.com  
Date: 2008.10.14 13:25:46 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

## Bishai, John

---

**From:** Bishai, John  
**Sent:** Monday, September 22, 2008 7:41 AM  
**To:** 'MTHO (Michelle Thompson)'  
**Subject:** NDA 22341 Information request

Hello Michelle,

We have received your submission of 17 Sep 08 with analyses of major adverse cardiovascular events. In our previous request, the Division had asked for analyses of the composite of myocardial infarction, stroke or cardiovascular death. We note that, in the list of terms included in your analyses, terms were also included for acute coronary syndrome, unstable angina, acute renal failure, and various heart failure and ECG change terms. We realize that your intent was to follow our request to include all event terms which might represent events in the requested composite. However, our intent was for a somewhat more specific set of included terms. Please repeat your analyses, using the list of terms from page 7 of your submission, but omitting the following terms:

- Acute coronary syndrome
- Angina unstable
- Cardiac failure
- Cardiac failure congestive
- Right ventricular failure
- Electrocardiogram Q wave abnormal
- Electrocardiogram ST segment depression
- Electrocardiogram ST-T change
- Renal failure acute
- Pulmonary edema

Please perform these analyses on the set of all randomized controlled trials of liraglutide. Provide separate analyses for serious adverse events, and for combined serious + nonserious events. Comparisons should include all liraglutide vs all non-liraglutide, liraglutide vs placebo, and liraglutide vs active control. Provide information on the incidence of the endpoint by liraglutide dose.

Thanks,  
John

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/s/

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John M Bishai  
10/8/2008 08:54:36 AM  
CSO

NDA Amendment



October 07, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated September 22, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the September 22, 2008 request received from John Bishai, FDA Project Manager, to provide re-analyses of the Major Adverse Cardiovascular Events (MACE) using a specific set of terms.

At this time, Novo Nordisk is providing the requested information as an Amendment to the NDA 22-341.

This submission is being provided electronically (approximately 3 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5396 created on October 01, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609) 919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US,  
o=Novo Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.10.07 12:12:29 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



October 03, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated September 04, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to a September 04, 2008 email from John Bishai, FDA Project Manager with a Clinical Pharmacology reviewer request for information.

At this time, Novo Nordisk is providing the requested information under Module 5.3.3.5, (Population PK Study reports and related information) as an Amendment to the NDA 22-341.

This submission is being provided electronically (approximately 8 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5396 created on October 01, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,

NOVO NORDISK INC.

Sandra C. Cottrell,  
Ph.D. on behalf of  
Mary Ann  
McElligott, Ph.D.

Digitally signed by Sandra C. Cottrell, Ph.D.  
on behalf of Mary Ann McElligott, Ph.D.  
DN: cn=Sandra C. Cottrell, Ph.D. on behalf  
of Mary Ann McElligott, Ph.D., o=US,  
ou=Novo Nordisk Inc., ou=Regulatory Affairs,  
email=sacr@novonordisk.com  
Date: 2008.10.03 13:42:15 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.





**DSI CONSULT**

**Request for Biopharmaceutical Inspections**

**DATE:** October 1, 2008

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** (Required for international inspections)  
Director, Review Division, HFD-510 or


Director, Division of Pharmaceutical Evaluation, HFD-510

**FROM:** John Bishai, Regulatory Project Manager, HFD-510

**SUBJECT:** Request for Biopharmaceutical Inspections  
NDA 22-341  
Victoza (Liraglutide) Injection

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
NN2211-1692	Clinical Pharmacology Phase I Unit, Lund University Hospital, Lund, Sweden	

**b(4)**

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain): The study is pivotal in supporting BE of the Phase 3 and to be marketed formulation.

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **February, 1 2009**. We intend to issue an action letter on this application by **March 23, 2009**.

Should you require any additional information, please contact John Bishai.

Concurrence: (Optional)

Sally Choe Clinical Pharmacology Team Leader

Manoj Khurana Clinical Pharmacology Reviewer

*Below are the specifics regarding the desired site to be inspected.*

**Clinical Trial Site and Principal Investigator Details:**

**6 Investigators and Study Administrative Structure**

**Trial Site**

The trial was conducted at the Clinical Pharmacology Phase I Unit, Lund University Hospital, Lund, Sweden.

All the investigators, their affiliations and curricula vitae are listed in Appendix 16.1.4.

The following investigator was designated the signatory investigator for the trial:

Edward Högestätt, M.D., Ph.D.  
Medical Director Phase I Unit  
Dept. of Clinical Chemistry and Pharmacology  
Lund University Hospital  
SE-221 85 Lund  
Sweden

**Contract Research Organisation**

The following contract research organisation (CRO) was used:

**b(4)**

The primary contact person and the local trial manager at \_\_\_\_\_ was

**b(4)**

Liraglutide  
 Trial ID: NN2211-1692  
 Clinical Trial Report  
 Report Body

CONFIDENTIAL

Date: 05 October 2007  
 Version: 1.0  
 Status: Final  
 Page: 2 of 164

Novo Nordisk

## 1 Title Page

Title of Trial	A randomized, double-blind, single-centre, two-period, cross-over trial in healthy subjects investigating the bioequivalence between the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4).
Trial ID	NN2211-1692
Development Phase	Phase 1
Trial Registration ID no.	Not applicable
IND Number (US only)	Not applicable
EudraCT Number	2006-004283-31
Japanese Trial Number	Not applicable
Generic Name	Liraglutide
Indication	Type 2 Diabetes Mellitus
Investigator	Edward Högestätt, M.D., Ph.D., Dept. of Clinical Chemistry and Pharmacology, Lund University Hospital, Lund, Sweden
Trial Site	Clinical Pharmacology, Phase I Unit, Lund University Hospital, Lund, Sweden
Trial Initiated	29 January 2007
Trial Completed	16 April 2007
Sponsor	Novo Nordisk A/S, Global Development, DK-2880 Bagsvaerd, Denmark
International Medical Officer	Milan Zdravkovic, M.D., Ph.D., M.Sc. Pharm. Med., Novo Nordisk A/S
International Trial Manager	Monika Malm-Erjefält, Ph.D., Novo Nordisk A/S
Local Trial Manager	Agnes Görtz, B.Sc. (Pharm), TFS Trial Form Support
Trial Statisticians	Eva Usón B.Sc., TFS Trial Form Support and Charlotte Hindsberger Ph.D., Novo Nordisk A/S
Trial Medical Writer	Hanna Liedman, Ph.D., TFS Trial Form Support
Report Date	05 October 2007

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice <sup>1, 2</sup>.

**Analytical Site Details:**

\_\_\_\_\_ **b(4)**  
CT Project: 2006-E-603  
Trial ID: NN2211-1692  
Phase: 1  
Liraglutide

Date: 2007-06-19  
Page 1 of 92  
Version no. 1  
Status: Final

**BIOANALYTICAL REPORT**

Author:

\_\_\_\_\_ **b(4)**

Organization:

\_\_\_\_\_ **b(4)**

Sponsor: Novo Nordisk A/S  
Krogshøjvej 55  
DK-2880 Bagsværd  
Denmark

Trial ID: NN2211-1692

Trial title: A randomized, double-blind, single center, two-period, cross-over trial in healthy subjects investigating the bioequivalence between the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4).

CT project no.: 2006-E-603

Title: Analytical Determination of Liraglutide in Plasma Samples from Trial ID NN2211-1692

CT Project: 2006-E-603  
Trial ID: NN2211-1692  
Phase: I  
Liraglutide

Date: 2007-06-19  
Page 5 of 92  
Version no. 1  
Status: Final

**GENERAL INFORMATION**

**Test Facility:**

**Dates:** Start of experimental work: 2007-03-21  
End of experimental work: 2007-05-09

**Personnel involved in the study**

**Sponsor:** Novo Nordisk A/S  
Krogshøjvej 55  
DK-2880 Bagsværd  
Denmark

**Sponsor contact:** Monika Malm-Erjefält  
Novo Nordisk A/S  
Krogshøjvej 55  
DK-2880 Bagsværd  
Denmark

**Principal investigator:** Poul Persson (PP)  
Capio Diagnostik a.s.

b(4)

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/s/

-----  
John M Bishai  
10/1/2008 02:58:35 PM



NDA 22-341

INFORMATION REQUEST LETTER

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 July 22, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

We are reviewing the Clinical Pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please submit the following datasets to support the population analysis conducted under NN2211-1573:

- All datasets used for model development and validation should be submitted as a 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.

If you have any questions, call John Bishai, Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



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this page is the manifestation of the electronic signature.**  
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/s/  
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Mary Parks  
9/30/2008 02:49:30 PM

**Bishai, John**

---

**From:** Bishai, John  
**Sent:** Monday, September 29, 2008 2:43 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** Aljuburi, Lina  
**Subject:** Information/sample request for NDA 22-341 Novo's Victoza

Dear Michelle,

During the review of your application (NDA 22-341), our reviewers have the following requests:

- Please submit samples of the 3 mL cartridge as well as the Pen-injector intended for use with their drug product (Liraglutide 6.0 mg/ml)
- Please submit working samples of both the labeled \_\_\_\_\_ (Please note: the samples previously submitted were non-functioning models.)
- Please samples with properly functioning needles. As part of our review, we would like to simulate the use of each pen.
- Please send a sample of the carton labeling for \_\_\_\_\_ pens. Although a carton label sample has been submitted, the reviewer would like to see how the \_\_\_\_\_ pens are packaged in each container. \_\_\_\_\_  
\_\_\_\_\_ To eliminate any confusion, seeing an actual carton with its contents would greatly help our understanding.

b(4)

If you have any questions or concerns, feel free to contact me.

Thanks,  
John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: john.bishai@fda.hhs.gov  
Tel: 301.796.1311  
Fax: 301.796.9712

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
John M Bishai  
9/29/2008 02:51:20 PM  
CSO



**TRANSMITTED BY FACSIMILE**

James N. Czaban  
Counsel to Eastbourne Capital  
1875 Pennsylvania Avenue NW  
Washington, DC 20006

**RE: Promotion of liraglutide (investigational new drug)**

Dear Mr. Czaban:

The Division of Drug Marketing, Advertising, and Communications received your complaint letter dated August 6, 2008, regarding promotional activities by Novo Nordisk (Novo) regarding its investigational new drug, liraglutide.

Thank you for your assistance in bringing this matter to our attention. We have considered your complaint in light of the materials you submitted and, based on our preliminary review, some of the issues appears to have merit. Therefore, we will take this matter into further consideration and take appropriate action as deemed necessary.

Please be advised that our review of this matter is ongoing. You may obtain information about the status of your complaint only after a determination is made not to take action and the matter is closed, or after such action has occurred and the matter is closed.

We appreciate your concern and encourage you to bring to our attention other promotional materials that you believe to be false or misleading. If you have any additional information about this matter, please contact me by facsimile (301) 847-8444, or write to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705. We remind you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising, and Communications

-----  
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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Sam Skariah  
9/25/2008 05:01:29 PM



**TRANSMITTED BY FACSIMILE**

Cheryl Watton, MD  
Executive Director, Regulatory Affairs and Safety  
Amylin Pharmaceuticals, Inc.  
9360 Towne Centre Drive  
San Diego, CA 92121

**RE: Promotion of liraglutide (investigational new drug)**

Dear Dr. Watton:

The Division of Drug Marketing, Advertising, and Communications received your complaint letter dated July 16, 2008, regarding promotional activities by Novo Nordisk (Novo) regarding its investigational new drug, liraglutide.

Thank you for your assistance in bringing this matter to our attention. We have considered your complaint in light of the materials you submitted and, based on our preliminary review, some of the issues appear to have merit. Therefore, we will take this matter into further consideration and take appropriate action as deemed necessary.

Please be advised that our review of this matter is ongoing. You may obtain information about the status of your complaint only after a determination is made not to take action and the matter is closed, or after such action has occurred and the matter is closed.

We appreciate your concern and encourage you to bring to our attention other promotional materials that you believe to be false or misleading. If you have any additional information about this matter, please contact me by facsimile (301) 847-8444, or write to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705. We remind you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising, and Communications

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

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Sam Skariah

9/24/2008 02:24:24 PM

**NDA Amendment – 4-Month Safety Update**



September 23, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341**  
**Victoza® [liraglutide injection]**  
**NDA Amendment – 4-Month Safety Update**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in patients with type 2 diabetes. We are amending the NDA to provide a 4-month safety update as required under 21 CFR 314.50(d) (5)(vi)(b).

Additional patient exposure has been added to the safety database since the NDA. No clinically significant imbalances (liraglutide vs. non-liraglutide treatment) in adverse events or events of special interest (pancreatitis, thyroid events, neoplasms and immunogenicity) have been identified in this 4-month Safety Update database. Liraglutide is generally well tolerated. The most commonly reported side effects are related to the gastrointestinal system and are transient in nature which is consistent with what was reported in the ISS. Stratified statistical evaluations were conducted on the larger safety database to more thoroughly identify potential imbalances across treatment groups including increased focus on Major Adverse Cardiac Events (MACE).

The information presented in this safety update is consistent with the draft package insert submitted with the NDA. Therefore, there are no safety issues that would require updating of the originally submitted labeling at this time.

This Amendment includes updated accumulated safety information for all completed trials as of May 30, 2008. Two trials which were described as ongoing in the Integrated Summary of Safety (ISS) have been completed and safety data from these trials are included. The two completed trials were conducted in a Japanese population using doses different than the proposed U.S. label doses.

The Update also includes safety information for eight (8) trials ongoing as of May 30, 2008. Data from two (2) of these trials (NN2211-1572 and NN2211-1573) were provided in the original NDA (12 months and 18 months data respectively). Trial NN2211-1797 completed the main part of the study (26 weeks) and is ongoing in a 14-week extension. Summary results from this trial are presented below:

*NN2211-1797: Effect on glycemic control of liraglutide or exenatide added to metformin, sulfonylurea or a combination of both in subjects with type 2 diabetes. A 26-week randomized, open-label, active comparator, 2-armed, parallel-group, multi-center, multi-national trial with a 14-week non-randomized extension period.*



Summary of results:

	Liraglutide 1.8 mg <i>qd</i> +OAD	Exenatide 10ug <i>bid</i> +OAD
Intent-to-treat population (N)	233	231
HbA1c (%) (Mean)		
Baseline	8.2	8.1
Change from baseline	-1.12	-0.79
FPG (mmol/L) Mean		
Baseline	9.78	9.47
Change from baseline	-1.61	-0.60
Body Weight (kg) Mean		
Baseline	93.1	93.0
Change from baseline	-3.24	-2.87

Safety data from other ongoing trials: NN2211-1572 (ext), NN2211-1573 (ext), NN2211-1796, NN2211-1700 (ext), NN2211-1701 (ext) and NN8022-1807 (ext) are included in this update. Please note NN8022-1807 is a trial in obese non-diabetic patients.

In this Safety Update, we have assessed the effect of liraglutide on major adverse cardiovascular events (MACE) in the clinical development program. The rates of occurrence of MACE, non-serious and serious, were similar across the liraglutide and control treatment groups. There was no dose-dependency in the occurrence of MACE in the liraglutide treated groups. A Cox regression analysis showed no significant treatment difference across treatments and Kaplan-Meier plots of time from randomization to event showed no difference across treatment groups. Taken together - the data with liraglutide on MACE supports, based on the Cox Proportional Hazard model, that with a probability of 95% the estimated interval [0.36; 1.77] contains the hazard ratio between liraglutide and placebo.

In response to the Advisory Committee meeting on 01-02 July 2008 regarding general cardiovascular risk assessment for drugs for treatment of Type 2 diabetes, Novo Nordisk has thoroughly considered what actions to take in relation to liraglutide. As stated above, we have not identified any cardiovascular adverse signal in the development program of liraglutide. We have, however, decided to address the Advisory Committee's general recommendation regarding adequate assessment of the cardiovascular risk by committing to perform a post-approval randomized and controlled phase IV cardiovascular clinical study to exclude risk at a predetermined level.

Our preliminary design considerations are in accordance with the recommendations from the Advisory Committee meeting in July 2008, and we would appreciate the opportunity to further discuss such a phase IV commitment with the Agency at your earliest convenience.

Therefore, at this time, we are amending the Risk Management Plan (RMP) submitted with the original NDA. The amended RMP reflects the above mentioned commitment to perform a post-approval cardiovascular study. This amendment is provided as a new leaf in the CTD structure and placed in Module 1.

This submission is being provided electronically (approximately 750 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5386 created on September 17, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Michelle  
Thompson**

Digitally signed by Michelle Thompson  
DN: cn=Michelle Thompson, c=US,  
o=Novo Nordisk Inc., ou=Regulatory  
Affairs, email=mtho@novonordisk.com  
Date: 2008.09.23 08:32:21 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



September 17, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information dated August 21, 2008**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the August 21, 2008 request received from John Bishai, FDA Project Manager, to provide analyses of the Major Adverse Cardiovascular Events (MACE).

At this time, Novo Nordisk is providing the requested information as an Amendment to the NDA 22-341.

This submission is being provided electronically (approximately 2 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5384 created on September 15, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann**  
**McElligott**  
Digitally signed by Mary Ann  
McElligott  
DN: cn=Mary Ann McElligott,  
c=US, o=Novo Nordisk,  
ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.09.17 15:42:31 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

## Bishai, John

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**From:** Bishai, John  
**Sent:** Thursday, September 04, 2008 2:29 PM  
**To:** 'MTHO (Michelle Thompson)'  
**Cc:** Aljuburi, Lina  
**Subject:** Information request for NDA 22-341

Dear Michelle,

During the review process, the Clinical Pharmacology team had the following information request:

Please submit the following datasets to support the population analysis conducted under study NN2211-1573:

- All datasets used for model development and validation should be submitted as a 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.

Submission of the aforementioned would help provide a more thorough review of your application. If you have any questions or concerns, please feel free to contact me.

Thanks,  
John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: john.bishai@fda.hhs.gov  
Tel: 301.796.1311  
Fax: 301.796.9712

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

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John M Bishai  
9/4/2008 03:29:28 PM  
CSO

**NDA Amendment**



August 25, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information (Filing Communication Letter)**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 to FDA for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to the 74 day filing letter received from the FDA dated August 05, 2008.

At this time, Novo Nordisk is providing the requested information addressed in that letter as an Amendment to the NDA 22-341.

This submission is being provided electronically (approximately 1 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5368 created on August 22, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Sandra C. Cottrell,**  
Ph.D. on behalf of  
**Mary Ann McElligott,**  
Ph.D.

Digitally signed by Sandra C. Cottrell, Ph.D. on behalf of Mary Ann McElligott, Ph.D.  
DN: cn=Sandra C. Cottrell, Ph.D. on behalf of Mary Ann McElligott, Ph.D., c=US, o=Novo Nordisk Inc., ou=Regulatory Affairs, email=scc@novonordisk.com  
Date: 2008.08.25 15:28:10 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



August 14, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Raw Data Listing for Study NN2211-1572**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes.

As required under 21 CFR 314.50(f)(1), the original NDA contained individual patient tabulations with the study reports. However, as a result of a minor publishing error, the Raw Data Listing for study NN2211-1572 submitted in the original NDA did not contain complete listings for all patients. At this time, we are providing the complete Raw Data Listing for all patients in study NN2211-1572.

This submission is being provided electronically (approximately 175 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5358 created on August 11, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Sandra C. Cottrell, Ph.D.**  
Digitally signed by Sandra C. Cottrell, Ph.D.  
on behalf of Mary Ann McElligott, Ph.D.  
DN: cn=Sandra C. Cottrell, Ph.D., on behalf of  
Mary Ann McElligott, Ph.D., c=US, o=Novo  
Nordisk Inc., ou=Regulatory Affairs,  
email=scotr@novonordisk.com  
Date: 2008.08.14 14:40:54 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-341

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 new drug application (NDA) dated and received on May 23, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Victoza (liraglutide injection).

We also refer to your NDA Amendment dated June 18, 2008 which included a response to FDA request for information.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 23, 2009.

We also request that you submit the following information:

- A. The drug substance and drug product specifications should be revised to list the biologically active product-related substances individually and with individual acceptance criteria.
- B. The drug product specification should be revised to include Filling Volume, with a footnote that this is an in-process test.
- C. The proposed acceptance criteria for Filling Volume is greater than or equal to  $\frac{1}{10}$  mL per cartridge. It is not clear whether the lower limit will be adequate to ensure that the patient will get 10 doses of 1.8 mg of product per dose (as labeled) if some volume is required for \_\_\_\_\_ the pen injector. USP <1151> requires a filling volume in slight excess of the labeled volume in order to permit withdraw and administer the labeled volume. Provide a justification for the lower limit of Filling Volume.
- D. Provide a justification for the lack of leachables testing in the drug product specification and stability studies when up to \_\_\_\_\_ leachables were found in the leachables and extractables studies.

b(4)



- E. Your comparability protocols for the post-approval addition of a drug product manufacturer and addition of a manufacturer for the assembly of the pen injectors are under review. Be advised that such a protocol may not be appropriate for downgrading the submission of a manufacturer of an aseptically processed sterile product to the proposed category of an annual report.

Please respond only to the above requests for additional 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.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application for pediatric patients for patients below 10 years of age. We also acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients 10- / years of age.

**b(4)**

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,  
{See appended electronic signature page}

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

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Mary Parks

8/5/2008 03:50:14 PM

## DSI CONSULT: Request for Clinical Inspections

**Date:** 7/10/2008

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46  
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47  
Susan Leibenhaut, M.D.

**Through:** Karen Mahoney, M.D., F.A.C.E / Division of Metabolism and Endocrinology  
Products /HFD-510  
Hylton Joffe, M.D., M.M.Sc., Team Leader /Division of Metabolism and  
Endocrinology Products /HFD-510

**From:** John Bishai Ph.D., Regulatory Health Project Manager/Division of  
Metabolism and Endocrinology Products/HFD-510

**Subject:** Request for Clinical Site Inspection(s)

### **I. General Information**

Application#: NDA-22,341  
Sponsor/Sponsor contact information (to include phone/email): Novo Nordisk  
Drug: Victoza (liraglutide)  
NME: Yes  
Standard or Priority: Standard  
Study Population < 18 years of age: No  
Pediatric exclusivity: No

PDUFA:  
Action Goal Date: 3/23/2009  
Inspection Summary Goal Date: **31 Dec 08**

### **II. Background Information**

Originally, liraglutide injection, a GLP-1 analog, was submitted on October 5, 2000 as IND 61,040. This investigational new drug was developed as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. NDA number 22-341 (NDA Type-1) was issued by the division on February 11, 2008.

A clinical concern with this product is a possible risk for thyroid cancer and elevated serum calcitonin. Complete ascertainment of this adverse event is very important. At whatever site(s) the DSI team choose(s), please look for any evidence that there were cases of thyroid cancer or elevated

calcitonin that were not included in the NDA submission. This would be in addition to the usual items for which the DSI team routinely inspects.

**III. Protocol/Site Identification**

The Division of Metabolism and Endocrinology Products suggests inspection of one or more of the following sites. These are suggestions; the Division of Scientific Investigations may use discretion in the choice of site(s).

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Luis Rivera-Colon CARR 21 S 3-2 Las Lomas, Rio Pedras Puerto Rico	1573	23	Improve glycemic control in type 2 diabetes mellitus.
Gregory Peterson, DO 411 Laurel St, Suite 3275 Des Moines, IA 50314	1574	19	Same
Matatoshi Kikuchi Institute for Adult Diseases Life Foundation Marunouchi Hospital Tokyo, Japan	1334	11	Same
Aila Rissanen Helsinki University Central Hospital 00260 Helsinki Finland	1807	114	Same

**IV. Site Selection/Rationale**

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Significant equity interest (Dr. Peterson, >\$50,000).

**International Inspections:**

Reasons for inspections (please check all that apply):

Page 3-Request for Clinical Inspections

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) Dr. Leibenhaut of DSI requested identification of foreign sites for possible inspection. Dr. Rissanen's site enrolled more patients than any other site in the development program. Dr. Kikuchi received large "Significant Payments of Other Sorts" (\$95,833 in "donations" and \$14,362 in honoraria).

**Five or More Inspection Sites:**

Not applicable.

Should you require any additional information, please contact John Bishai (RPM) at 301-796-1311 or Karen Mahoney (Medical Officer) at 301-796-1250.

Concurrence:

Hylton Joffe, M.D., M.M.Sc. Medical Team Leader  
Karen Mahoney M.D., F.A.C.S., Medical Reviewer  
Mary Parks, M.D., Director, Division Director

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

-----  
John M Bishai  
8/5/2008 04:18:29 PM

NDA Amendment



July 11, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes.

At this time, Novo Nordisk is providing the requested clinical information in this submission. The Agency requested to submit the information to the diabetes IND (61,040) and the \_\_\_\_\_

b(4)

This submission is being provided electronically (approximately 25 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5335 created on July 09, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at dlgr@novonordisk.com.

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at mtho@novonordisk.com, or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Lewis R. Pollack**  
on behalf of M.  
McElligott

Digitally signed by Lewis R. Pollack on  
behalf of M. McElligott  
DN: cn=Lewis R. Pollack on behalf of M.  
McElligott, c=US, o=Novo Nordisk, Inc.,  
ou=Regulatory Affairs,  
email=LEWP@novonordisk.com  
Date: 2008.07.11 12:20:29 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

NDA Amendment



July 08, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to an email received on June 20, 2008 from Anthony L. Parola, FDA Pharmacologist requesting historical control data found in mouse and rat carcinogenicity studies of liraglutide.

At this time, Novo Nordisk is providing the following information in this submission:

- Historical control data for all neoplasms found in 2 year mouse and rat carcinogenicity studies.
- Historical control data for tumors in subcutaneously dosed 2 year mouse and rat carcinogenicity studies.
- Historical control data for microchip implanted mice and rats.

This submission is being provided electronically (approximately 25 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.0.0, virus definition file version 5333 created on July 07, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Sandra C. Cottrell,**  
Ph.D. on behalf of  
Mary Ann McElligott,  
Ph.D.

Digitally signed by Sandra C. Cottrell, Ph.D.  
on behalf of Mary Ann McElligott, Ph.D.  
DN: cn=Sandra C. Cottrell, Ph.D., on behalf  
of Mary Ann McElligott, Ph.D., c=US,  
o=Novo Nordisk Inc., ou=Regulatory Affairs,  
email=scott@novonordisk.com  
Date: 2008.07.08 14:52:41 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



NDA Amendment



June 18, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 22-341  
Victoza® [liraglutide injection]  
NDA Amendment – Response to FDA request for information**

Dear Dr. Parks:

Reference is made to NDA 22-341, Victoza [liraglutide injection] submitted on May 23, 2008 for FDA review and approval for treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to an email received on June 11, 2008 from John Bishai, FDA Regulatory Project Manager requesting additional ecg raw datasets from study NN221-1644.

Enclosed, we are providing an ecg raw dataset which includes the information requested. The dataset is provided as SAS.xpt with a define.pdf file consistent with the dataset formatting in the original submission.

This submission is being provided electronically (approximately 97 MB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.00v.4.5.1 SP1, virus definition file version 5318 created on June 16, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US,  
o=Novo Nordisk, ou=Regulatory  
Affairs, email=MAAMC@NovoNordisk.  
com  
Date: 2008.06.17 17:45:07 -0400

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.



**TRANSMITTED BY FACSIMILE**

Mr. James N. Czaban  
Counsel to Eastbourne Capital  
Wilmer Cutler Pickering Hale and Dorr LLP  
1875 Pennsylvania Avenue NW  
Washington, D.C. 20006

**RE: Promotion of liraglutide**

Dear Mr. Czaban:

The Division of Drug Marketing, Advertising, and Communications received your complaint letter dated May 13, 2008, regarding promotional activities by Novo Nordisk for its investigational drug candidate liraglutide.

Thank you for your assistance in bringing this matter to our attention. We have considered your complaint in light of the materials you submitted and, based on our preliminary review, some of the issues appear to have merit. Therefore, we will take this matter into further consideration and take appropriate action as deemed necessary.

Please be advised that our review of this matter is ongoing. You may obtain information about the status of your complaint only after a determination is made not to take action and the matter is closed, or after such action has occurred and the matter is closed.

We appreciate your concern and encourage you to bring to our attention other promotional materials that you believe to be false or misleading. If you have any additional information about this matter, please contact me by facsimile (301) 847-8444, or write to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705. We remind you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising, and Communications

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

/s/

-----  
Sam Skariah

7/3/2008 05:03:40 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>FOOD AND DRUG ADMINISTRATION</b>	<b>PRESCRIPTION DRUG USER FEE COVERSHEET</b>				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdufa/default.htm">http://www.fda.gov/cder/pdufa/default.htm</a>					
<b>1. APPLICANT'S NAME AND ADDRESS</b>  NOVO NORDISK PHARMACEUTICALS INC Patricia Robson 100 College Road West Princeton NJ 08540 US	<b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b>  22-341				
<b>2. TELEPHONE NUMBER</b> 609-919-7790	<b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
<b>3. PRODUCT NAME</b> liraglutide	<b>6. USER FEE I.D. NUMBER</b> PD3008261				
<b>7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</b>  <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
<b>8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</b>					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:  <table style="width:100%; border: none;"> <tr> <td style="width: 33%; border: none;">                             Department of Health and Human Services                              Food and Drug Administration                              CBER, HFM-99                              1401 Rockville Pike                              Rockville, MD 20852-1448                         </td> <td style="width: 33%; border: none;">                             Food and Drug Administration                              CDER, HFD-94                              12420 Parklawn Drive, Room 3046                              Rockville, MD 20852                         </td> <td style="width: 33%; border: none;">                             An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.                         </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
<b>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</b>  Mary Ann McElligott <div style="font-size: x-small; margin-top: 5px;">                     Digitally signed by Mary Ann McElligott                      DN: cn=Mary Ann McElligott, o=CDER, ou=Novo Nordisk, ou=Regulatory Affairs, email=MAAC@NovoNordisk.com                      Date: 2008.05.13 15:18:25 -0700                 </div>	<b>TITLE</b> Associate Vice President, Regulatory Affairs	<b>DATE</b>  May 23, 2008			
<b>9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION</b> \$1,178,000.00					
Form FDA 3397 (03/07)					

[Close](#) [Print Cover sheet](#)



ORIGINAL NDA SUBMISSION

May 23, 2008

Mary Parks, M.D., Director  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: Original NDA Submission  
NDA 22-341  
Victoza® [liraglutide injection]**

Dear Dr. Parks:

Reference is made to IND 61,040 for liraglutide, a GLP-1 analog, submitted on October 5, 2000 for investigational treatment as an adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes. Reference is also made to NDA number 22-341 issued by the Agency on February 11, 2008 for the electronic submission of this New Drug Application (NDA).

This submission is an original NDA for this product. Liraglutide (INN and USAN adopted name ref. Module 1.15) is a new molecular entity and is a once-daily, human GLP-1 analog with 97% homology to native human GLP-1. Liraglutide has a protracted action profile based on 3 mechanisms: self-association, which results in slow absorption; binding to albumin and enzymatic stability towards DPP-IV and NEP enzymes resulting in a long plasma half-life.

We are filing for approval of this product in the following strengths/package presentations:

1.2 mg

1.8 mg

b(4)

We are applying for a drug product shelf life of \_\_\_\_\_ months at 2-8°C and for a drug substance shelf life of \_\_\_\_\_ months at \_\_\_\_\_ °C.

We are submitting the proposed trade name **Victoza®** for Division review and approval. This is the intended global trade name, already approved by the EMEA. The nomenclature research and analysis report from a study conducted by Drug Safety Institute establishing that **Victoza®** is not confusingly similar to existing drug names or names of related products is enclosed, and located in Module 1.15. A request for Division review and feedback on this proposed name was previously submitted to the IND on November 15, 2007, Amendment Serial number 218.

**Novo Nordisk Inc.**  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

The NDA contains draft labeling for the physician's package insert (annotated), patient inserts, cartons (including sample carton, business reply, and reminder prescription sticker), and pen labeling. Additionally, as required, we are including the physician insert in Structured Product Labeling (SPL) format. Draft labeling is included in Module 1.14.

The User Fee for this submission in the amount of \$1,178,000, was submitted on May 5, 2008 (the User Fee Cover sheet identifying User Fee ID Number PD 3007135 is included with this application) and receipt acknowledged by the Agency on May 6, 2008. A debarment statement, Investigator Financial Disclosure Information, and Patent Certification are included.

Additionally, a letter of Authorization to Type V DMF \_\_\_\_\_, which contains information on \_\_\_\_\_ is provided in Module 1.4.1.

b(4)

This submission consists of the 5 Modules in the Common Technical Document (CTD) structure. It is formatted as an electronic Common Technical Document (eCTD) according to FDA Guidances for Industry documents on content and CTD format, as well as ICH-CTD guidances. A field copy is not required for an electronic NDA submission and will not be provided to the district office.

Based on the anticipated FDA receipt date of this application, the 4-month Safety Update will be provided to the Agency by September 23, 2008.

The following briefly summarizes major agreements made with the Division of Metabolism and Endocrinology Products and Novo Nordisk regarding the filing of this application:

**1) End of Phase 2/Pre-NDA Meeting Discussions**

**(a) Chemistry, Manufacturing and Controls**

Drug substance stability: As proposed in the Pre-NDA meeting package and accepted by the Division, this application contains the following:

	Storage Temperature	
	-18 °C ± 2 °C	5 °C ± 3 °C
Supportive stability data Pilot Plant _____	30 months	12 months
Primary stability data Pilot Plant _____	18 months	12 months
Production Plant stability data _____	3 months	3 months

b(4)

We will amend the NDA file during the review period to provide additional 24 months primary stability data (from 3 pilot batches), 6 months primary stability data (from 3 production batches) and 7 months supportive stability data from the 3 ongoing supportive batches. We anticipate amending the file with this additional data within 6 months of this submission.

b(4)

Drug product stability: As proposed in the Pre-NDA meeting package and accepted by the Division, this application contains the following:

	Storage Temperature		
	5 °C ± 3 °C	25 °C ± 2 °C	37 °C ± 2 °C
Supportive Stability Batches: Pilot Scale/ Production Dept	24 months	6 months	3 months
Primary stability batches: Pilot Scale/ Production Dept	18 months	6 months	3 months
Production Scale/Production Dept.	3 months	3 months	3 months

b(4)

We will amend the NDA file during the review period to provide additional 24 months primary stability data (from pilot batches), 6 months primary stability data (from production batches) and 7 months supportive stability data from the 3 ongoing supportive batches. We anticipate amending the file with this additional data within 6 months of this submission.

b(4)

Comparability Protocols: As proposed in the Pre-NDA meeting package and accepted by the Division, this application includes comparability protocols to support the following changes:

- Manufacture (formulation and filling) of drug product at a second site previously FDA-approved for other production. The manufacturing process to be used at this second site is the same as described in Module 3 of this application.
- Assembly of drug product in pen-injector at a second FDA approved Novo Nordisk manufacturing site.

The changes will be implemented post-approval and will be reported as identified by the Division.

**(b) Preclinical**

This application includes carcinogenicity studies conducted in the rat and in the mouse. The protocols for these studies were submitted via Special Protocol Assessment (IND 61,040 Serial number 02 and Serial number 40 respectively). Full study reports are provided in Module 4, 4.2.3.4 and TUMOR.XPT data from these studies are provided in datasets folders identified by study number. Preclinical studies included with this submission were conducted in accordance with current ICH and FDA guidelines.

**(c) Clinical**

As discussed and agreed to at the February 5, 2008 Pre-NDA meeting, this application includes the following:

- As requested by FDA at the May 4, 2004 End of Phase 2 Meeting, Novo Nordisk conducted a thorough QT prolongation study (NN2211-1644). The final study report including protocol, annotated CRF and associated datasets and programs (provided in .SAS and pdf format) are located in Module 5, 5.3.4. The completed Highlights of Clinical Pharmacology table can be found in the study report folder. Additionally the liraglutide Investigator's Brochure, Edition 9, dated 28 April 2008 is located in Module 1, 1.14.4.1. The digital ECGs generated during the course of this study have been uploaded to the Mortara ECG Warehouse and FDA will be notified of the availability of these data.
- Individual Patient Tabulation as required under 314.50(f)(1) are provided in Module 5, within the individual study report folders.
- As discussed and addressed in the Division's April 2, 2008 letter, we are providing full datasets for phase 2 and phase 3 trials and selected datasets (all adverse event information, pharmacokinetic/pharmacodynamic data, laboratory safety parameters, treatment and exposure data) for phase 1 trials. A define.pdf document which is provided with each study dataset, includes the additional items as requested in the April 2, 2008 letter.
- Case Report Forms (CRFs) for patients who died, withdrew due to an adverse event or experienced a serious adverse event are provided in Module 5, within the individual study report folders. Additionally as requested we are providing CRFs for adverse events of special interest (pancreatitis, Immunogenicity and for any subject with a thyroid event). Narratives for deaths, withdrawals due to non-serious adverse events, serious adverse events, and adverse events of interest (significant immunological reactions, thyroid tumors and pancreatitis) are provided in Module 5, 5.3.5.3 Appendix 7.5, Listings 1 and 2.
- A complete Integrated Summary of Safety (ISS) including associated Tables, Appendices and datasets is located in Module 5.3.5.3. However, as provided for under draft Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document (June 2007), the text of the Integrated Summary of Efficacy is incorporated into the Summary of Clinical Efficacy, Module 2.7.3. However, consistent with the guidance, the associated Tables, Appendices and datasets are located in Module 5.3.5.3

**(d) Pediatric Studies:**

As agreed to at the End of Phase 2 meeting and discussed again during the February 5, 2008 Pre-NDA meeting, we are requesting a waiver for children under 10 years and a deferral for children 10 to 17 years. The request for deferral in this application includes an outline of our pediatric plan and descriptions of studies to be conducted in pediatric subjects.

b(4)



**(e) Administrative/Formatting Issues**

- As requested to facilitate clinical reviewer selection of clinical sites for inspection, tables for each of the completed Phase 3 clinical trials are included in this file. The tables for completed Phase 3 clinical trials (including investigator information and protocol deviations) are located in Module 1,
- Tables providing site and investigator information for each study supporting the safety and efficacy of the NDA are included in Module 1, 1.3.4. Signed Form FDA 3454 and 3455 are included as well.

**2) Risk Management Plans**

As we indicated during the Pre-NDA meeting, we are providing a Risk Management Plan (RMP) as part of this original application. This risk management plan with a data lock point of February 21, 2008 was prepared in accordance with current ICH/FDA guidance. The document consists of two parts. The first part focuses on the current knowledge of the safety profile of liraglutide and the pharmacovigilance plan, which details the established and planned pharmacovigilance procedures within Novo Nordisk to manage product risk. The second part of the RMP is the evaluation of the need for risk minimization activities for liraglutide based on the product profile. The proposed risk minimization activities outlined in the document which include routine pharmacovigilance activities, appropriate professional product labeling text, and continued surveillance of spontaneously reported cases, of events of interest in ongoing and planned clinical trials we believe to be adequate based on the current knowledge of the safety profile of liraglutide.

This submission is being provided electronically (approximately (13 GB) in e-CTD structure with an XML backbone. The electronic files have been virus scanned and determined to be virus free. The software used for virus checking is McAfee VirusScan Enterprise 8.00v.4.5.1 SP1, virus definition file version 5295 created on May 14, 2008. Should you have any questions regarding the technical electronic aspects of this submission, please contact Dominique Lagrave, Director, Regulatory Operations and Innovation, at (609)919-7891 or via e-mail at [dlgr@novonordisk.com](mailto:dlgr@novonordisk.com).

Should you have any questions regarding this submission, please contact Michelle Thompson, Director, Regulatory Affairs at 609-987-5972, via email at [mtho@novonordisk.com](mailto:mtho@novonordisk.com), or via fax at 609-987-3916.

Sincerely,  
NOVO NORDISK INC.

**Mary Ann  
McElligott**

Digitally signed by Mary Ann McElligott  
DN: cn=Mary Ann McElligott, c=US, o=Novo  
Nordisk, ou=Regulatory Affairs,  
email=MAMC@NovoNordisk.com  
Date: 2008.05.19 16:42:13 -04'00'

Mary Ann McElligott, Ph.D.  
Associate Vice President, Regulatory Affairs

Sent via FDA Gateway

Please note that Novo Nordisk Inc. considers this NDA and all correspondence related thereto as confidential, proprietary trade secret information and hereby claims protection from disclosure under the applicable section of 18 USC and Title 21 of the Code of Federal Regulations.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

Form Approved: OMB No. 0910-0338  
Expiration Date: September 30, 2008  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Novo Nordisk Inc.		DATE OF SUBMISSION 05/23/2008	
TELEPHONE NO. (Include Area Code) 609-987-5831		FACSIMILE (FAX) Number (Include Area Code) 609-987-3961	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 College Road West, Princeton, NJ 08540		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)			22-341
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) liraglutide		PROPRIETARY NAME (trade name) IF ANY Victoza	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) human GLP-1 analog		CODE NAME (If any) NNC 90-1170	
DOSAGE FORM: solution for injection	STRENGTHS: 6 mg/ml	ROUTE OF ADMINISTRATION: subcutaneous injection	
(PROPOSED) INDICATION(S) FOR USE: An adjunct therapy to diet and exercise to improve glycemic control in patients with type 2 diabetes.			

**APPLICATION DESCRIPTION**

APPLICATION TYPE (check one)		<input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug		Holder of Approved Application	
TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> PRESUBMISSION	<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT	
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER	
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION Original NDA			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED		THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC	

**ESTABLISHMENT INFORMATION** (Full establishment information should be provided in the body of the Application.)  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Sites are ready for inspection. See file 356h-continuation.pdf for manufacturing site information.  
Contact Person: Lise Lundbeck, Corporate Vice President, Quality Systems Surveillance, Novo Nordisk, Denmark  
Phone: (45) 44 42 8771, Fax: (45) 44 42 8799

**Cross References** (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 61, 040  
DMF Number — Novo Nordisk Inc. — Validation information

b(4)

This application contains the following items: <i>(Check all that apply)</i>		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling <i>(check one)</i>	<input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input checked="" type="checkbox"/>	4. Chemistry section	
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER <i>(Specify)</i>	FDA Form 3674, DMF Letter, Meeting Background Inform., Pediatric Inform., Environ. Analysis, IB, Risk Manag. Plan
<b>CERTIFICATION</b>		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.</li> <li>5. Regulations on making changes in application in FD&amp;C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.</li> <li>6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p><b>Warning:</b> A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		DATE:
Mary Ann McElligott <small>Digitally signed by Mary Ann McElligott DN: cn=Mary Ann McElligott, o=FDA, email=mary.ann.mcelligott@hhs.gov</small>		05/23/2008
TYPED NAME AND TITLE		
Mary Ann McElligott, PhD , Assoc. Vice President, Reg. Affairs		
ADDRESS <i>(Street, City, State, and ZIP Code)</i>		Telephone Number
100 College Road West, Princeton, NJ 08540		609-987-5831
<p><b>Public reporting burden for this collection of information</b> is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

**APPLICANT INFORMATION** This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

**PRODUCT DESCRIPTION** This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

**APPLICATION INFORMATION** If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

**TYPE OF SUBMISSION** should be indicated by checking the appropriate box:

**Original Application** = a complete new application that has never before been submitted;

**Amendment to a Pending Application** = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

**Resubmission** = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

**Presubmission** = information submitted prior to the submission of a complete new application;

**Annual Report** = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

**Establishment Description Supplement** = supplements to the information contained in the Establishment Description section (#15) for biological products;

**Efficacy Supplement** = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

**Labeling Supplement** = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

**Chemistry, Manufacturing, and Controls Supplement** = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

**Other** = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

**Submission of Partial Application** Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

**CBE "Supplement-Changes Being Effected"** supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

**CBE-30** "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

**Prior Approval (PA)** "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

**REASON FOR SUBMISSION** This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

**NUMBER OF VOLUMES SUBMITTED** Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

**This application is**

Paper  Paper and Electronic  Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

**ESTABLISHMENT INFORMATION** This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

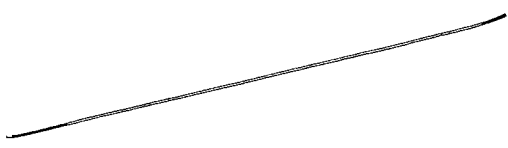
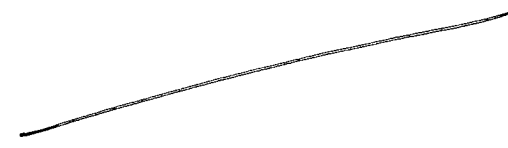
**CROSS REFERENCES** This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

**Items 1 through 20 on the reverse side of the form** constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

**Signature** The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

**Table 1 Drug Substance Establishment Information**

<b>Manufacturing Location</b>	<b>Activity</b>
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark  <b>FEI Number: 3002807751</b> <b>CFN Number: FCDA69</b>	
Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark  <b>FEI Number: 3001392218</b> <b>CFN Number: FCDA039</b>	
Novo Nordisk A/S Sydmarken 5 DK-2860 Søborg Denmark  <b>FEI Number: N/A</b> <b>CFN Number: N/A</b>	Quality Control of in-process samples and drug substance.

**b(4)**

**Table 2 Drug Product Establishment Information**

Manufacturing Location	Activity
Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark  <b>FEI Number: 3001392218</b> <b>CFN Number: FCDA039</b>	Formulation, filling and inspection of bulk drug product. Quality control of in-process samples and bulk drug product.
Novo Nordisk A/S Ndr. Fasanvej 215 DK-2000 Frederiksberg Denmark  <b>FEI Number: N/A</b> <b>CFN Number: N/A</b> (not manufacturing facility)	Quality control of bulk drug product.
Novo Nordisk A/S Brennum Park DK-3400 Hillerød Denmark  <b>FEI Number: 3003131673</b> <b>CFN Number: FCDA070</b>	Assembly, labeling and packaging of finished drug product. Quality control of bulk drug product and finished drug product.
Novo Nordisk A/S Hallas Allé DK-4400 Kalundborg Denmark  <b>FEI Number: 3002807751</b> <b>CFN Number: FCDA69</b>	Labeling and packaging of finished drug product.
Novo Nordisk Pharmaceutical Industry, Inc. 3612 Powhatan Road Clayton, North Carolina 27520, United States  <b>FEI Number: 1000158576</b> <b>CFN Number: 1058438</b>	Labeling and packaging of finished drug product.



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
Food and Drug Administration

**Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with  
Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))**

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

**SPONSOR / APPLICANT / SUBMITTER INFORMATION**

1. NAME OF SPONSOR/APPLICANT/SUBMITTER Novo Nordisk Inc.	2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES 05/23/2008
3. ADDRESS (Number, Street, State, and ZIP Code) 100 College Road West Princeton, NJ 08540	4. TELEPHONE AND FAX NUMBER (Include Area Code) (Tel.) (609) 987-5831 (Fax) (609) 987-3916

**PRODUCT INFORMATION**

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)  
**FOR DEVICES:** Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)  
(Attach extra pages as necessary)

Liraglutide (NNC 90-1170)

**APPLICATION / SUBMISSION INFORMATION**

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES  
 IND     NDA     ANDA     BLA     PMA     HDE     510(k)     PDP     Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER (If number previously assigned)  
22-341

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES  
000

**CERTIFICATION STATEMENT / INFORMATION**

9. CHECK ONLY ONE OF THE FOLLOWING BOXES (See instructions for additional information and explanation)

A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES (Attach extra pages as necessary) Extra pages attached

NCT Number(s): NCT00154401    NCT00294723    NCT00318461    NCT00318422    NCT00333151

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.  
**Warning:** A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)  Digitally signed by Mary Ann McElligott DN: cn=Mary Ann McElligott, o=US, o=Novo Nordisk, ou=Regulatory Affairs, email=MAMC@NovoNordisk.com Date: 2008.05.19 13:01:38 -04'00'  <b>Mary Ann McElligott</b>	12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11 (Name) Mary Ann McElligott, Ph.D. (Title) Associate Vice President, Regulatory Affairs
13. ADDRESS (Number, Street, State, and ZIP Code) (of person identified in No. 11 and 12) 100 College Road West Princeton, NJ 08540	14. TELEPHONE AND FAX NUMBER (Include Area Code) (Tel.) (609) 987-5831 (Fax) (609) 987-3916
	15. DATE OF CERTIFICATION 05/23/2008



### Instructions for Completion of Form FDA 3674

**Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))**  
Form 3674 must accompany an application/submission, including amendments, supplements, and resubmissions, submitted under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.

1. **Name of Sponsor/Applicant/Submitter** - This is the name of the sponsor/applicant/submitter of the drug/biologic/device application/submission which the certification accompanies. The name must be identical to that listed on the application/submission.
2. **Date** - This is the date of the application/submission which the certification accompanies.
3. & 4. - Provide complete address, telephone number and fax number of the sponsor/applicant/submitter.
5. **Product Information - For Drugs/Biologics:** Provide the established, proprietary name, and/or chemical/biochemical/blood product/cellular/gene therapy name(s) for the product covered by the application/submission. Include all available names by which the product is known. **For Devices:** Provide the common or usual name, classification, trade or proprietary or model name(s), and/or model number(s). Include all available names/model numbers by which the product is known.
6. **Type of Application/Submission** - Identify the type of application/submission which the certification accompanies by checking the appropriate box. If the name of the type of application/submission is not identified, check the box labeled "Other."
7. **IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/Other Number** - If FDA has previously assigned a number associated with the application/submission which this certification accompanies, list that number in this field. For example, if the application/submission accompanied by this certification is an IND protocol amendment and the IND number has already been issued by FDA, that number should be provided in this field.
8. **Serial Number** - In some instances a sequential serial number is assigned to the application. If there is such a serial number, provide it in this field.
9. **Certification** - This section contains three different check-off boxes.  
**Box A** should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply because no clinical trials are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies.  
**Box B** should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply at the time of submission to any clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, at the time the application/submission is being made, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply to any of the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies.  
**Box C** should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do apply at the time of submission to some or all of the clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, at the time the application/submission is being made, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies.
10. **National Clinical Trial (NCT) Numbers** - If you have checked Box C in number 9 (Certification), provide the NCT Number obtained from [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) for each clinical trial that is an "applicable clinical trial" under 42 U.S.C. § 282(j)(1)(A)(i), section 402(j)(1)(A)(i) of the Public Health Service Act, and that is included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. Type only the number, as NCT will be added automatically before number. Include any and all NCT numbers assigned to the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies. Multiple NCT numbers may be required for a particular certification, depending on the number of "applicable clinical trials" included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies.
11. **Signature of Sponsor/Applicant/Submitter or an Authorized Representative** - The person signing the certification must sign in this field.
12. **Name and Title of Person Who Signed in number 11.** - Include the name and title of the person who is signing the certification. If the person signing the certification is not the sponsor/applicant/submitter of the application/submission, he or she must be an authorized representative of the sponsor/applicant/submitter.
13. & 14. - Provide the full address, telephone and fax number of the person who is identified in number 11 and signs the certification in number 11.
15. Provide the date the certification is signed. This date may be different from the date provided in number 2.

#### Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/submission) per response, including time for reviewing instructions. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to the applicable address below.

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
Form No. FDA 3674  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
Center for Devices and Radiological Health  
Program Operations Staff (HFZ-403)  
9200 Corporate Blvd.  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a currently valid OMB control number.*

NCT00331851  
NCT00154414  
NCT00422058  
NCT00480909  
NCT00393718  
NCT00395746  
NCT00518882  
NCT00620282  
NCT00614120

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 25, 2005  
**TIME:** 10:00 to 11:00 am  
**LOCATION:** Teleconference  
**APPLICATION:** IND 61,040  
**DRUG NAME:** Liraglutide  
**TYPE OF MEETING:** Type C; Guidance

**MEETING CHAIR:** John Dietrick

**MEETING RECORDER:** Lina AlJuburi, Pharm.D., M.S.

### **FDA ATTENDEES:** (Title and Office/Division)

John Dietrick	Team Leader, Office of Compliance, Foreign Inspection Team
Zi Qiang Gu, Ph.D.	Compliance Officer, Investigations & Pre-approval Compliance Branch
Stephen Moore, Ph.D.	Chemistry Team Leader
Xavier Ysern, Ph.D.	Chemistry Reviewer
Christine Moore, Ph.D.	Branch Chief, Manufacturing Sciences, Office of New Drug Quality Assurance (ONDQA)
Ted Chang, Ph.D.	Reviewer, Manufacturing Sciences, ONDQA
Lina AlJuburi, Pharm.D.	Regulatory Project Manager, Division of Metabolism and Endocrinology Products

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### *Novo Nordisk Inc.*

Michael O'Reilly	Research Chemist
Michael Elleskov	Production Scientist
Michael de Bang	Production Project Manager
Henrik Block Schultz	Manager, Site Quality Assurance
Mette Uve Jars	Chemistry, Manufacturing, and Controls Project Manager
Sandra Auguste-Bowler	Chemistry, Manufacturing, and Controls Regulatory
Finn Møllgaard	Regulatory
Jimmy Tan	Regulatory
Michelle Thompson	Regulatory

### **BACKGROUND:**

IND 61,040 for Liraglutide (NNC 90-1170) Injection was submitted on October 5, 2000. Liraglutide is a modified GLP-1 peptide analog manufactured using recombinant DNA technology. It is under investigation as adjunct therapy to diet and exercise to improve glycemic control and manage body weight in subjects with type 2 diabetes. Liraglutide is a new molecular entity. It is administered as a subcutaneous (s.c.) injection using a modified \_\_\_\_\_

Liraglutide is at the end of Phase 2/start of Phase 3 of their clinical development program.

A CMC meeting was requested to discuss the proposed process validation set up for the drug substance fermentation and recovery processes. The briefing package was included with the meeting request in a submission dated August 9, 2005. An amendment to the briefing package to revise question 2 was submitted on October 18, 2005.

**MEETING OBJECTIVES:**

To discuss the proposed process validation set up for the drug substance fermentation and recovery processes

**DISCUSSION POINTS:**

The Sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

**Question 1: General PV Set-Up for the Fermentation and Recovery Processes**

~~\_\_\_\_\_~~

**b(4)**

**Yes, the Sponsor's proposal for the process validation set-up for the fermentation and recovery process appears to be acceptable.**

**Question 2: Fermentation PV**

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

**b(4)**

If the failure is not process related, (e.g., mechanical, human error) then the Sponsor's proposal is acceptable. Standard operation procedures to demonstrate that the failure is not process related will need to be established a priori.

Question 3: Proposed Recovery PV Set-Up

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b(4)

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1 Page(s) Withheld

√ Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Yes, the Agency agrees with this definition provided that historical records can provide traceability for everything that went into the batch.

**Additional Comment:**

The FDA was concerned whether the frequency of testing the fermentation is sufficient to ensure that the sublots collected can be combined. ✓

✓ This is acceptable.

b(4)

Comments provided by the Agency during this teleconference are based on the proposals provided in the briefing package. Execution of these plans will have to be evaluated at the time of inspection.

Minutes preparer: Lina AlJuburi  
Chair concurrence: John Dietrick

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Lina Aljuburi  
11/23/2005 01:24:29 PM



## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** September 20, 2005  
**TIME:** 10:00 to 10:30 am  
**LOCATION:** Teleconference  
**APPLICATION:** IND 61,040  
**DRUG NAME:** Liraglutide (NN2211) Injection  
**TYPE OF MEETING:** Type C; Guidance

**MEETING CHAIR:** David Orloff, M.D.

**MEETING RECORDER:** Jena Weber

### **FDA ATTENDEES:** (Title and Office/Division)

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Eddie Gabry, M.D.	Medical Officer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer
Jena Weber	Regulatory Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES:**

*Novo Nordisk Inc.*

Peter Kristensen	Project Management
Milan Zdravkovic	Medical Development
Rickey Reinhardt	Clinical Research
Soren Dyring Jacobsen	Preclinical Development
Lars Wichmann Madsen	Toxicology
Lotte Bjerre Knudsen	Toxicology
Finn Møllgaard	Regulatory
Jimmy Tan	Regulatory
Michelle Thompson	Regulatory

### **BACKGROUND:**

IND 61,040 for Liraglutide (NNC 90-1170) Injection was submitted on October 5, 2000. Liraglutide is a modified GLP-1 peptide analog manufactured using recombinant DNA technology. It is under investigation as adjunct therapy to diet and exercise to improve glycemic control and manage body weight in subjects with type 2 diabetes. Liraglutide is a new molecular entity. It is administered as a subcutaneous (s.c.) injection using a modified \_\_\_\_\_

b(4)

On February 26, 2004, the Division held a teleconference with the sponsor, at the sponsor's request, to discuss the preliminary findings from the 2-year rat carcinogenicity studies. The sponsor stated that 2-year rat toxicity studies indicated an increased frequency of C-cell tumors in the thyroid. C-cell adenoma was found in all the dose groups. C-cell carcinoma was seen at a

lower significance. Thyroid tumors were detected at week 40 in early descendent rats; the cause of death was unknown. Based on the neoplastic thyroid findings in the rat carcinogenicity study, the Division recommended clinical monitoring of calcium, calcitonin, vitamin D, PTH, plasma and urine calcium levels, plasma and urine phosphorous levels, thyroid ultrasound (at screening, during the trial, and annual follow-up for at least 2 years,) TSH, T3 and T4 is prudent with repeated clinical dosing.

Additional discussion took place at the End-of-Phase 2 meeting held on May 4, 2004, and a teleconference on November 23, 2004.

This teleconference was requested on July 15, 2005, and the meeting information package was submitted on August 22, 2005.

#### **MEETING OBJECTIVES:**

To discuss the initiation of Phase 3 of the liraglutide drug development program.

#### **DISCUSSION POINTS:**

The Sponsor requested responses to the following questions. The questions are repeated below and the responses are bolded.

#### ***Question 1 and Follow-up to Question 1:***

Based on

- a) the substantiated mechanism of action behind the rodent C-cell findings
- b) the proposed clinical safety monitoring program, and
- c) conditional upon the results from the ongoing medium term clinical study (NN2211-1571) not showing a C-cell safety signal after un-blinding the data

Novo Nordisk considers it safe to proceed into phase 3a studies, and considers that the rodent C-cell findings are unlikely to pose a risk to the involved study subjects in the proposed phase 3a studies.

As liraglutide (NN2211) is a global development project, question 1 was recently discussed with the Danish Medicines Agency (DKMA). The conclusion was that provided no safety signals are seen in the current phase 2b trial, DKMA found it highly unlikely that the rodent C-cell findings are of human relevance. Thus, DKMA will accept that Novo Nordisk proceeds into phase 3.

Given the preclinical data that show the C-cell findings are rodent specific it was concluded that this was of no human relevance and therefore, a specific withdrawal of patients with elevated calcitonin is not needed from a safety perspective and the exclusion of patients with elevated calcitonin or family history of thyroid diseases was not recommended by the DKMA. It was suggested only to measure calcitonin along with routine evaluation of other safety laboratory tests, as a minimum at the beginning and end of the trial. As for other laboratory parameters it should be at the discretion of the investigator to determine if a patient should be included / continue in the trial should calcitonin values be found to be out of the normal range and if additional clinical evaluation should be performed.

Following careful consideration Novo Nordisk proposes implementing this approach in the long term clinical studies.

*Does the Agency agree to this approach?*

It is acceptable to proceed cautiously into Phase 3a studies without calcitonin monitoring at 12 week intervals after unblinding of the data from the 14-week European Phase 2 Study NN2211-1571, entitled *Effect on glycemic control of three doses of liraglutide in monotherapy versus placebo in subjects with type 2 diabetes. A 14-week, double-blind, randomized, parallel-group, multi-center, international trial*, provided that it yields additional evidence of a lack of liraglutide effect on calcitonin release.


The available information is not yet sufficient to rule out the potential human relevance of the rodent C cell findings. Unstimulated calcitonin measurement is not particularly sensitive to detect C-cell hyperplasia in humans. The Division urges the Sponsor to perform a (pentagastrin) stimulated calcitonin test on a subset of subjects in Phase 3a at baseline and at the end of the study. Because of its sensitivity to detect C-cell hyperplasia, stimulated calcitonin measurement would demonstrate that the suspected liraglutide effect on the thyroid C-cell was adequately worked up in the trial of longest duration. No pentagastrin IND would be deemed necessary to do a pentagastrin stimulation test in the context of these trials.

The Division concurs that the exclusion of patients with elevated calcitonin or family history of thyroid diseases is not warranted. The Sponsor will submit the final clinical trial reports for Study NN221-1551, entitled *A randomized, double-blind, single centre, placebo-controlled, 21-day multiple s.c. doses, dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide (NNC 90-1170) in healthy Japanese male subjects*, and Study NN221-1591, entitled *A randomized, double-blind within dose group, single-centre, placebo controlled, parallel 2-different dose group, 14-day multiple s.c. doses study to assess the safety, pharmacokinetics and pharmacodynamics of liraglutide (NNC-90-1170) in subjects with type 2 diabetes*.

### Change to Phase 3 Program

Novo Nordisk has previously proposed a phase 3 program to support the following indication:

**b(4)**

Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is indicated as monotherapy or in combination with metformin or a sulfonylurea when diet, exercise or the single agent does not result in adequate glycemic control. 

### **Question 2:**

The trials and trial designs to support the proposed indication have been accepted by EU and US regulatory authorities. The company has decided to apply for an additional indication of liraglutide in combination with metformin and a sulfonylurea. The following study is designed to support this indication:

**Trial 1697 – 26 week study**

**Table 1–1 Trial design**

		A N = 228	Liraglutide 1.8 mg/day	+ metformin 2000 mg + glimepiride 2-4 mg	
Screen 2 weeks	Forced metformin 2000 mg + glimepiride 4 mg titration 3 + 3 weeks	B N = 114	Liraglutide placebo	+ metformin 2000 mg + glimepiride 2-4 mg	Follow-up 1 week
		C N = 228	Insulin glargine variable dose	+ metformin 2000 mg + glimepiride 2-4 mg	

- a) *Is the proposed trial and trial design adequate to support the liraglutide combination with metformin and a sulfonylurea indication?*

**The trial design seems adequate to support the proposed indication of liraglutide combination with metformin and a sulfonylurea.**

- b) *This study will be conducted at 4 mg top dose of glimepiride which is not the maximally approved US dose. Is the comparator dose acceptable to support the indication?*

**The 4 mg top dose of glimepiride in the proposed trial seems appropriate, given the possible increased risk of hypoglycaemia when a sulfonylurea is administered in combination with a GLP-1 agonist.**

Minutes preparer: Lina AlJuburi  
Chair concurrence: David Orloff

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/s/

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Lina Aljuburi  
10/18/2005 04:53:12 PM

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 26, 2004  
**TIME:** 9:00 am to 9:45 am  
**LOCATION:** Teleconference  
**APPLICATION:** IND 61,040  
**DRUG NAME:** Liraglutide (NNC 90-1170) Injection  
**TYPE OF MEETING:** Type C; Guidance

**MEETING CHAIR:** Karen Davis-Bruno, Ph.D.

**MEETING RECORDER:** Lina AlJuburi, Pharm.D.

### FDA ATTENDEES:

Karen Davis-Bruno, Ph.D.	Supervisory Pharmacologist
Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510	

### EXTERNAL CONSTITUENT ATTENDEES:

Michelle Thompson	Regulatory Affairs (Princeton)
Mary Ann McElligott	Regulatory Affairs (Princeton)
Lene Thrane	Regulatory Affairs (Denmark)
Kristian Tage Hansen	Project Management (Denmark)
Milan Zdravkovic	Medical Development (Denmark)
Soren Dyring Jacobsen	Toxicology (Denmark)
Lars Wichmann Madsen	Toxicology (Denmark)

### BACKGROUND:

IND 61,040 for Liraglutide (NNC 90-1170) Injection was submitted on October 5, 2000. It is a GLP-1 analog under investigation as adjunct therapy to diet and exercise to improve glycemic control and manage body weight in subjects with type 2 diabetes. Liraglutide is a new molecular entity, currently at the end-of-phase 2 in its clinical development. An end-of-phase 2 meeting was requested on February 27, 2004, and is scheduled for May 3, 2004.

### MEETING OBJECTIVES:

To discuss the preliminary findings from the 2-year carcinogenicity studies, the planned studies to elucidate these findings and to obtain Division input on the planned approach.

### DISCUSSION POINTS:

The sponsor stated that 2-year rat toxicity studies indicated an increased frequency of C-cell tumors in the thyroid. C-cell adenoma was found in all the dose groups. C-cell carcinoma was

seen at a lower significance. Anti-calcitonin was used to make the C-cell diagnosis. Thyroid tumors were detected at week 47 in early descendent rats, the cause of death was unknown.

According to the sponsor, the 62-week monkey study and the 26-week rat study did not demonstrate any pre-neoplastic findings. A 2-year mouse carcinogenicity study has not been conducted, because ICH S6 (Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals) states that only one animal carcinogenicity study is necessary and the sponsor chose the rat.

The sponsor stated that they plan to do a 4-6 week study in an attempt to establish the mechanism causing the thyroid tumor in rats. Establishing a rat specific mechanism of thyroid tumor formation in the absence of liver enzyme induction was discussed. Furthermore demonstrating a lack of human relevance would be a difficult task. The sponsor was also told that a study 4-6 weeks in length would probably not be long enough since thyroid tumors did not appear until week 47. It was made clear to the sponsor that mechanistic studies are useful to evaluate the relevance of tumor findings in animals for human safety but will not be sufficient to demonstrate that the thyroid tumors are specific to rats and will not be seen in humans. The sponsor clarified that their working hypothesis involved an increased biosynthesis of calcitonin in rats treated with liraglutide as responsible for the thyroid tumors seen. However, it was noted that marketed products that result in elevations in calcium, calcitonin and PTH are not associated with an increased incidence of thyroid tumors in rodents.

Clinical trials conducted in the U.S. and Europe include a 12-week study of Liraglutide administered once daily to subjects with type 2 diabetes with the highest dose group of 0.75 mg/day.

Future plans for clinical studies were also discussed. The sponsor plans to conduct a 2-year clinical study with doses up to 2 mg/day and a 6-week clinical study in subjects with type 2 diabetes with doses up to 1.9 mg/day.

The sponsor has two ongoing clinical trials in Japan with liraglutide treatment for up to three weeks duration where they are monitoring serum calcium, PTH, calcitonin, vitamin D and thyroid hormone. There are currently no ongoing clinical trials in the U.S. or Europe.

#### **ACTION ITEMS:**

After consulting with members of the clinical team in DMEDP and based on the neoplastic thyroid findings in the rat carcinogenicity study, clinical monitoring of calcium, calcitonin, vitamin D, PTH, plasma and urine calcium levels, plasma and urine phosphorous levels, thyroid ultrasound (at screening, during the trial, and annual follow-up for at least 2 years,) TSH, T3 and T4 is prudent with repeated clinical dosing.

Minutes Preparer: Lina AlJuburi, Pharm.D.

Regulatory Project Manager

Chair Concurrence: Karen Davis-Bruno, Ph.D.

Supervisory Pharmacologist

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this page is the manifestation of the electronic signature.**  
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/s/

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Lina Aljuburi  
3/8/04 03:17:09 PM



## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-341 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Victoza Established/Proper Name: Liraglutide Dosage Form: Injection		Applicant: Novo Nordisk Agent for Applicant (if applicable): Mary Ann McElligott
RPM: John Bishai		Division: DMEP
<p><b>NDAs:</b>            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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated            Date of check:</p> <p><b>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.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		May 22, 2009 May 23, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <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  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	0/5/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ 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> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain 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.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	
<b>Officer/Employee List</b>	
❖ 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
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s)
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	01/11/10
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	05/23/08
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	01/13/10

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	12/10/09
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	5/23/08
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	11/16/09
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	12/28/09
<ul style="list-style-type: none"> <li>❖ Proprietary Name                             <ul style="list-style-type: none"> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	01/13/10
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK 01/13/10 <input checked="" type="checkbox"/> DDMAC 10/26/09 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 01/13/10
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	08/4/08
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable 08/05/09
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable 10/07/09
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 06/26/09
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 02/05/08
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 09/20/05

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• 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>)</li> </ul>	<input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<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	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ○ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation



○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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