

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206321Orig1s000

OTHER REVIEW(S)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

PMR/PMC Description: A juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity.

PMR/PMC Schedule Milestones: Final Report Submission: December 2014

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

A juvenile animal study with liraglutide is considered necessary to assess for potential adverse outcomes or irreversible adverse effects on growth, learning/memory/behavioral development, and sexual maturation as a result of exposure during pre-pubertal and pubertal period. These data are not necessary to support approval of this drug for use in adults.

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.”

Repeat-dose studies of long-acting glucagon-like peptide (GLP)-1 receptor agonists in monkeys suggest that these drugs may accelerate the onset of puberty or the rate of maturation of males. In 52-week and 87-week studies of liraglutide in monkeys, most males were sexually immature at study initiation. In these studies, testes weight trended higher in liraglutide-treated male monkeys at clinically relevant exposures over the study duration. Transient exposure of immature rodents to GLP-1 receptor agonists can cause behavioral and endocrine changes that persist into adulthood. The goal of the juvenile animal toxicity study with Saxenda is to assess its potential to cause adverse effects in animals treated from pre-puberty through reproductive maturity.

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

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

PMR/PMC Description: A clinical pharmacology study (Trial NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

PMR/PMC Schedule Milestones: Final Report Submission: December 2014

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

Saxenda is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

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.”

The goal of this study is to establish the pharmacokinetics and pharmacodynamics of Saxenda in the pediatric subpopulation ages 12-17 (inclusive) to determine appropriate dosing to be used in a subsequent efficacy/safety study.

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 clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.*

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

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

PMR/PMC Schedule Milestones: Final Protocol Submission: August 2015
Study/Trial Completion: August 2019
Final Report Submission: August 2020

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

Saxenda is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

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.”

The goal of this study is to establish the safety and efficacy of Saxenda in the pediatric subpopulation ages 12-17 (inclusive).

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 56-week randomized, double-blind-placebo-controlled pediatric study to evaluate the safety and efficacy of Saxenda in pediatric patients ages 12-17 years (inclusive). The study population should consist of pediatric patients with obesity, ages ≥ 12 to ≤ 17 years, with one or more weight-related co-morbidities (controlled hypertension, diabetes, or dyslipidemia) with BMI above the 95th percentile based on age and sex. Subjects with genetic or endocrine causes of obesity should be excluded. Adequate representation from both male and female adolescents should be included and subjects must have a documented history of failure to lose sufficient weight with lifestyle modification alone. Safety assessments should include monitoring for neoplasms, pancreatitis, gallbladder disease, increases in calcitonin, hypoglycemia, increases in heart rate, immunogenicity, and psychiatric adverse events.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.*

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

PMR/PMC Description: A clinical pharmacology study to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

PMR/PMC Schedule Milestones: Final Protocol Submission: September 2015
Study/Trial Completion: August 2017
Final Report Submission: August 2018

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

Saxenda is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

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.”

The goal of this study is to establish the pharmacokinetics and pharmacodynamics of Saxenda in the pediatric subpopulation ages 7-11 (inclusive) to determine appropriate dosing to be used in a subsequent efficacy/safety study.

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 clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.*

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

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

PMR/PMC Schedule Milestones: Final Protocol Submission: April 2020
Study/Trial Completion: October 2023
Final Report Submission: August 2024

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

Saxenda is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

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.”

The goal of this study is to establish the safety and efficacy of Saxenda in the pediatric subpopulation ages 7-11 (inclusive).

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 56-week randomized, double-blind-placebo-controlled pediatric study to evaluate the safety and efficacy of Saxenda in pediatric patients ages 7-11 years (inclusive). The safety and efficacy study should enroll children, ages 7 - 11 years (inclusive), with age- and sex-matched BMI \geq 99th percentile with a major co-morbidity. Subjects must have a documented history of failure to lose sufficient weight with comprehensive multidisciplinary intervention. Subjects with obesity associated with known endocrine or genetic causes should be excluded. Safety assessments should include monitoring for neoplasms, pancreatitis, gallbladder disease, increases in calcitonin, hypoglycemia, increases in heart rate, immunogenicity, and psychiatric adverse events. This study will not be initiated until results from the adolescent safety and efficacy trial have been submitted and reviewed by the Agency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

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

PMR/PMC Schedule Milestones: Final Protocol Submission: June 2015
Study/Trial Completion: September 2030
Final Report Submission: September 2031

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

Based on nonclinical studies, glucagon-like peptide-1 (GLP-1) agonists have been associated with 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.”

The goal of the registry is to detect the majority of cases of medullary thyroid carcinoma (MTC) that occur in the United States over the 15-year period after marketing approval of Saxenda, to evaluate all cases for risk factors for MTC and for exposure to diabetes medications, and to determine whether there is a relationship between Saxenda exposure and risk for MTC.

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 that seeks to identify all possible cases of MTC that occur in North America during the fifteen-year period after approval of Saxenda. 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 MTC and for exposure to Saxenda. Analyses will be conducted to determine whether Saxenda appears to be a risk factor for MTC. Reporting is to occur annually.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.*

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2015</u>
	Study/Trial Completion:	<u>September 2015</u>
	Final Report Submission:	<u>April 2016</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

The evaluation of the signal of a serious risk of breast cancer requires long-term safety data.

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.”

The goal of this PMR is to evaluate a signal of a serious risk of breast cancer.

In four Saxenda clinical trials, including extension, positively adjudicated breast cancer was reported in 14 (0.6%) of 2379 Saxenda-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (11 Saxenda- and 2 placebo-treated women) and ductal carcinoma *in situ* (3 Saxenda- and 1 placebo-treated woman). The majority of cancers were estrogen- and progesterone-receptor positive. There were too few cases to determine whether these cases were related to Saxenda. In addition, there are insufficient data to determine whether Saxenda has an effect on pre-existing breast neoplasia.

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.

This PMR requires the collection of information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the cardiovascular outcomes trial (LEADER), including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy. The LEADER trial is an ongoing randomized, double-blind, controlled trial.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - 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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2015</u>
	Study/Trial Completion:	<u>March 2015</u>
	Final Report Submission:	<u>August 2015</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

The evaluation of the signal of a serious risk of breast cancer requires long-term safety data.

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.”

The goal of this PMR is to evaluate a signal of a serious risk of breast cancer.

In four Saxenda clinical trials, including extension, positively adjudicated breast cancer was reported in 14 (0.6%) of 2379 Saxenda-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (11 Saxenda- and 2 placebo-treated women) and ductal carcinoma *in situ* (3 Saxenda- and 1 placebo-treated woman). The majority of cancers were estrogen- and progesterone-receptor positive. There were too few cases to determine whether these cases were related to Saxenda. In addition, there are insufficient data to determine whether Saxenda has an effect on pre-existing breast neoplasia.

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.

This PMR requires the collection of information on baseline cancer risk and potential confounders for all identified cases of breast cancer in Trial 1839, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy. Trial 1839 is an ongoing randomized, double-blind, controlled trial with a 2-year extension period.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.*

(signature line for BLAs)

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.

NDA # 206321
Product Name: SAXENDA (liraglutide) injection

PMR/PMC Description: A study evaluating gallbladder ejection fractions in liraglutide treated subjects to further characterize the effect of liraglutide on gallbladder motility.

PMR/PMC Schedule Milestones: Final Protocol Submission: September 2015
Study/Trial Completion: January 2017
Final Report Submission: September 2017

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

The number of patients with AEs pertaining to the gallbladder was small compared to the overall population. Acute gallbladder disease was reported in 2.3% of liraglutide-treated patients vs. 0.9% of placebo-treated patients.

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.”

AEs pertaining to the gallbladder were observed in the Saxenda program: Acute gallbladder disease (e.g., cholelithiasis and/or cholecystitis) was reported in 2.3% of liraglutide-treated patients vs. 0.9% of placebo-treated patients. Most events were serious and led to cholecystectomy in liraglutide-treated patients. The imbalance between treatment groups persisted even when controlling for degree of weight loss, which suggests a weight loss-independent effect of the drug.

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.

Study assessing gallbladder motility.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Study assessing gallbladder motility.

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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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

/s/

JENNIFER R PIPPINS
12/23/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 15, 2014

To: Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): SAXENDA (liraglutide [rDNA origin] injection)

Dosage Form and Route: solution for subcutaneous use

Application Type/Number: NDA 206321

Applicant: Novo Nordisk Inc.

1 INTRODUCTION

On December 20, 2013, Novo Nordisk, Inc. submitted for the Agency's review an Original NDA submission for SAXENDA (liraglutide [rDNA origin] injection) solution for subcutaneous use with the indication of an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients. Liraglutide [rDNA origin] injection was initially approved January 25, 2010, under the tradename Victoza as NDA 22341 and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) on March 11, 2014, and March 10, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU)] for SAXENDA (liraglutide [rDNA origin injection] solution for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was submitted on July 22, 2014.

2 MATERIAL REVIEWED

- Draft SAXENDA (liraglutide [rDNA origin injection] MG and IFU received on December 20, 2013, and received by DMPP on October 1, 2014.
- Draft SAXENDA (liraglutide [rDNA origin injection] MG and IFU received on December 20, 2013 and received by OPDP on October 1, 2014.
- Draft SAXENDA (liraglutide [rDNA origin injection] Prescribing Information (PI) received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 1, 2014.
- Draft SAXENDA (liraglutide [rDNA origin injection] Prescribing Information (PI) received on December 20, 2013 revised by the Review Division throughout the review cycle, and received by OPDP on October 9, 2014.
- Approved VICTOZA (liraglutide [rDNA origin injection] comparator labeling dated June 13, 2013.
- Approved BELVIQ (locaserin hydrochloride) comparator labeling dated June 27, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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

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

/s/

SHARON W WILLIAMS
10/15/2014

KENDRA Y JONES
10/15/2014

LASHAWN M GRIFFITHS
10/15/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

*** This document contains proprietary information that cannot be released to the public***

DATE: August 21, 2014

FROM: QuynhNhu Nguyen, Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Julie Golden, Medical Officer, CDER/OND/ODEII/DMEP
Pat Madara, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 2062321**
Applicant: Novo Nordisk
Device Constituent: peninjector
Drug Constituent: Liraglutide
Intended Treatment: for weight loss maintenance
CDRH CTS Tracking No. 1300023

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.08.22 15:53:33 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S

Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ronald D. Kaye -S,
0.9.2342.19200300.100.1.1=1300110677
Date: 2014.08.22 16:44:58 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

CDRH Human Factors Review

Overview and Recommendation

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a consultative review from Center for Devices and Radiological Health's Human Factors Premarket Evaluation Team on the human factors study report submitted in NDA 206321, for the PDS290 peninjector platform intended to deliver Liraglutide subcutaneously for weight loss and maintenance.

A human factors validation study (UT115) was conducted with 129 adult/elderly overweight and obese individuals who are able to perform their own injections, and 34 healthcare professionals (HCPs), who might interact with the PDS290 liraglutide 3.0 mg peninjector, including 16 HCPs and 18 pharmacists. The level of training and training content provided to test participants in the study reflected training that patients will receive in actual use and included reviewing the IFU in detail and viewing an ancillary instructional video.

The study results of concern are described as follows:

- Needle stick injury: Six out of 145 participants experienced needle stick injuries each resulting in task failure during one of the three injection tasks. Novo Nordisk believes that the potential medical consequences of these needle stick injury task failures are insignificant.
- There were other use errors that could result in mis-dosing i.e. underdosing or overdosing. For example:
 - 25 participants did not flow check before first injection. Novo Nordisk believes that the omission of the checking the flow step with a new (b) (4) pen-injector could potentially lead to a single insignificant underdose.
 - 7 participants did not set the dose correctly. Novo Nordisk believes that the dose not set correctly use error (setting the dose counter one or more clicks before or past the prescribed dose) could potentially result in an underdose/overdose (each click of the dose counter equals to 0.06 mg of liraglutide)
 - 5 participants performed flow checks with dose and but did not reset the dose. Novo Nordisk believes that the clinical consequence of this use error (expelling some medication before injecting) could potentially result in an underdose with no significant medical consequences and therefore, an insignificant impact on the therapy.

Recommendation: The consultant is concerned that the six task failures/use errors that resulted in needle stick injuries that occurred during needle removal. While this is a known risk associated with this type of device, the consultant believes that both the IFU and training should emphasize and caution the user of possible needle stick injuries that could occur while removing the needle.

This consultant asked Dr. Patricia Beaston, a CDRH medical officer, for comment on the clinical consequences of mis-dosing i.e. underdosing or over-dosing seen with multiple use errors within the human factors validation study. Please see her memo in Appendix 2. Her recommendation stated that the primary clinical reviewer should be notified of the findings of the human factor testing. Based on the safety information in the NDA, he/she should determine if the instructions for dosing concomitant anti-diabetic medications and or glycemic monitoring in the approved labeling are sufficient to inform healthcare providers and patients on the risks of hypoglycemia or hyperglycemia in the event of overdosing or underdosing with liraglutide. As a result, this consultant defers the

determination on the clinical acceptability of Novo Nordisk's assessment of clinical significance of mis-dosing i.e. underdosing and overdosing on the therapeutic effects of this drug product. If the clinical reviewer determines that if mis-dosing can result in significant impact on the therapy, then the consult would recommend that Novo Nordisk implement additional mitigations to address those use errors.

CDRH Human Factors Review

Combination Product Device Information

Submission No.: IND 61477
Applicant: Pfizer
Device Constituent: Autoinjector
Drug Constituent: Diazepam
Intended Treatment: anti-epileptics

CDRH Human Factors Involvement History

- 5/29/2014: CDRH HFPMET was requested to review the human factors report included in the IND.
 - Cover Letter: <\\CDSESUB1\evsprod\IND061477\0003\m1\us\cover.pdf>
 - EDR Location: <\\CDSESUB1\evsprod\IND061477\0003>
- 8/14/2014: CDRH HFPMET provided review recommendation to CDER

Summary of Human Factors Validation Study

Novo Nordisk performed a human factors validation study (reference # UT115, DV3320-UT115-2013 NN Report). Prior to this study, a formative study was conducted, and design modifications for the PDS290 liraglutide 3.0 mg pen-injector were implemented to reduce use errors.

The validation study was conducted with 129 adult/elderly overweight and obese individuals who are able to perform their own injections, and 34 healthcare professionals (HCPs), who might interact with the PDS290 liraglutide 3.0 mg peninjector, including 16 HCPs and 18 pharmacists. The following table provides the breakdown of study participants:

User group	Number of participants	Age (range and mean)		Gender		Training		Injection experience	
		Range	Mean	Male	Female	Trained	Untrained	Experienced	Naive
Adults	64	26-64	46.2	25	39	33	31	33	31
Elderly	65	65-84	68.9	35	30	34	31	35	30
HCPs	34	25-66	47.5	11	23	0	34	N/A	N/A
Total	163	26-74	52	71	92	67	96	68	61

The level of training and training content provided to test participants in the study reflected training that patients will receive in actual use and included reviewing the IFU in detail and viewing an ancillary instructional video.

The operation sequence for using the peninjector is:

- Step 1: Pick the correct carton/pen-injector
- Step 2: Pen cap removal
- Step 3: Verification via label and cartridge holder that it is the correct pen
- Step 4: Check that the drug in the pen injector is clear and colorless
- Step 5: Needle mounting
- Step 6: Checking the drug flow (this step only applies before the first injection with a new pen)
- Step 7: Setting the intended dose (reversing the dose setting, if necessary)

- Step 8: Understand the EOC indication (feature ensuring that no larger dose can be dialled than that is left in the cartridge. This step only applies if the user is going to inject a dose larger than the remaining left in cartridge.)
- Step 9: Subcutaneous needle insert
- Step 10: Injecting the dose, keep the needle in the skin after the dose counter has returned to 0 and count slowly to 6
- Step 11: Needle removal and disposal of used needle
- Step 12: Pen cap mounting

The following table shows the use scenarios, associated tasks, and relative task priority.

Condition	Step to test	Test priority	Severity class*
Scenario 1 – User does not receive the correct drug due to mix-up (all user groups will be tested)			
Steps are performed at dispensing, e.g. at the pharmacy, and at home: Normal test conditions Untidy or illogical storage system (only for pharmacies)	Step 1: Pick the PDS290 liraglutide 3.0 mg carton/pen-injector.	1	S4 – S5
	Step 2: Pen cap removal (Not pharmacists.)	3 (<i>Not safety-related</i>)	S1 – S2
	Step 3: Verify via label and cartridge holder it is the correct pen (Not pharmacists)	1	S4 – S5
Scenario 2 – The user does not administer the injection as intended (all user groups will be tested except pharmacists)			
All steps performed at home: Normal test conditions Naturally present dexterity and visual impairments.	Step 2: Pen cap removal	3 (<i>Not safety-related</i>)	S1 – S2
	Step 3: Verify via label and cartridge holder that it is the correct pen	1	S4 – S5
	Step 4: Check that the drug is clear and colourless	2	S3
	Step 5: Needle mounting	2	S3
	Step 6: Checking the drug flow (this step only applies before the first injection with each new pen)	3 (<i>Not safety-related</i>)	S1 – S2
	Step 7: Setting the intended dose (reversing the dose setting, if necessary)	2	S3
	Step 8: Understand the EOC indication (feature ensuring that no larger dose can be dialled than is left in the cartridge. This step only applies if the user is going to inject a dose larger than the remaining left in cartridge.)	2	S3
	Step 9: Subcutaneous needle insert	3 (<i>Not safety-related</i>)	S1 – S2
	Step 10: Injecting the dose, including leaving the needle in the skin after the dose counter has returned to 0 and counting slowly to 6	2	S3
	Step 11: Needle removal and disposal of used needle	2	S3
Step 12: Pen cap mounting	3 (<i>Not safety-related</i>)	S1 – S2	

*The severity class is based on the worst case scenario of each step

The study results of concern are described as follows:

- Needle stick injury: Six out of 145 participants experienced needle stick injuries each resulting in task failure during one of the three injection tasks. Notably, all seven needle stick injuries occurred during needle removal. Four of the participants removed the used needle from the pen-injector, inserted the needle into the outer needle cap, and used a finger to press the needle into the outer needle cap, thereby incurring a needle stick injury from the back needle (i.e., the exposed needle inside the needle's base). One participant incurred two needle stick injuries when attempting to recap a used needle from the pen-injector during Task 6 (end-of-content). The other participant incurred a needle stick injury when he inadvertently removed the inner needle cap while attempting to remove the needle during Task 4 (normal injection). Two participants thought that recapping a needle would decrease the risk of incurring a needle stick injury. Novo Nordisk believes that the potential medical consequences of these needle stick injury task failures are insignificant.
- There were other use errors that could result in misdosing i.e. underdosing or overdosing. For example,
 - 25 participants did not flow check before first injection. The root cause analysis indicated that for four of the participants, it appeared that the flow check symbol's appearance and the flow check step in the IFU was not sufficiently noticeable. Novo Nordisk believes that the omission of the checking the flow step with a new (b) (4) pen-injector could potentially lead to a single insignificant underdose.
 - 7 participants did not set the dose correctly. The root cause analysis indicated that for these participants, users can inject unmarked doses i.e. when the dose counter is set to any position, rather than set to one of the five, marked (i.e., approved) doses. It should be noted that IFU Step 3 (Select your dose) states that "Only doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg can be selected with the dose selector" suggesting that the dose selector can only stop at the listed doses. Novo Nordisk believes that the dose not set correctly use error (setting the dose counter one or more clicks before or past the prescribed dose) could potentially result in an underdose/overdose (each click of the dose counter equals to 0.06 mg of liraglutide)
 - 5 participants performed flow checks with dose and but did not reset the dose. One participant dialled the prescribed dose, expelled the full dose into the air to check the flow, and then injected without re-setting the dose during Task 4 (normal injection). During Task 6 (end-of-content), she dialled the prescribed dose, expelled a portion of the dose, and then injected without resetting the dose counter to the prescribed amount. Three participants dialled the prescribed dose, expelled some into the air, and then injected without re-setting the dose during one or more than one injection tasks. One participant expelled some medication after dialling the prescribed 3.0 mg dose, and then did so again after dialling back to 1.8 mg during Task 5 (dose reversal). Four participants did not understand that they needed to check the flow before setting the dose. Novo Nordisk believes that the clinical consequence of this use error (expelling some medication before injecting) could potentially result in an underdose with no significant medical consequences and therefore, an insignificant impact on the therapy.

Appendix 1: Device Related Information

The PDS290 liraglutide, with the proposed brand name 6.0 mg/mL utilizes the PD290 pen-injector platform. Furthermore, the design is based on the same user interface concept as the currently marketed prefilled pen Victoza® pen-injector. The design is a pen-shaped injector with a prefilled cartridge, where the intended dose is given by turning the dose selector and pressing the dose button to deliver the intended dose. The PDS290 liraglutide 3.0mg pen-injector provides the users with a display of the number of milligrams deliver 0.6 mg, 1.2 mg, 1.8 mg, and 2.4 mg (titration) and 3.0 mg (maintenance).



Clinical Consult

Date: July 6, 2014

From: Patricia Beaston, M.D., Ph.D., Medical Officer

To: Quynh Nhu Nguyen, Human Factors Reviewer

Device: pre-filled, multi-dose pen

Drug: Liraglutide (Saxenda¹, NDA 206321) for obesity

Dosage: Solution for subcutaneous injection, doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg (6 mg/mL, 3 mL).

Sponsor: Novo Nordisk, Inc.

Finding: Question to be raised to the primary clinical reviewer.

Materials reviewed: Proposed labeling for Saxenda and approved labeling for Victoza.

Request: Human Factors reviewer asked for comment on the clinical consequences of under-dosing or over-dosing.

Response to request: The Sponsor has proposed a new indication for the drug liraglutide for the treatment of obesity. The dosing regimen will be up to 3.0 mg compared to up to 1.8 mg for liraglutide for diabetes. Rates of hypoglycemia were reported to be higher in studies enrolling patients with type 2 diabetes who were taking anti-diabetic medications. Any potential relationship between dose or treatment adherence was not mentioned in either the current (diabetes) or proposed (obesity) labeling.

Treatment with liraglutide results in delayed gastric emptying and increased-dosing/overdosing with liraglutide can result in nausea and vomiting both of which can affect glycemic control and response to diabetes treatment. Overdosing and underdosing can result in unpredictable results to the combined treatment for diabetes and cause hypoglycemia and hyperglycemia. There is a potential for increased effect with the higher possible dose of the new treatment regimen.

Recommendation:

The primary clinical reviewer should be notified of the findings of the human factor testing. Based on the safety information in the NDA, he/she should determine if the instructions for dosing concomitant anti-diabetic medications and or glycemic monitoring in the approved

¹ Also, currently marketed as Victoza (NDA 22341) for adults with type 2 diabetes at doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

labeling are sufficient to inform healthcare providers and patients on the risks of hypoglycemia or hyperglycemia in the event of overdosing or underdosing with liraglutide.

Background Information (excerpted from the labeling):

Drug Substance:

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs. Endogenous GLP-1 has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-4 and NEP.

Missed dose instructions:

If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make-up for the missed dose.

(b) (4) patients should be advised to reinitiate Saxenda at 0.6 mg if more than 3 days have elapsed since the last Saxenda dose. (b) (4) gastrointestinal symptoms associated with reinitiation of treatment.

Overdosage instructions:

Overdoses have been reported in clinical trials and post-marketing use of liraglutide. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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

/s/

PATRICIA J MADARA

09/28/2014

Checking in CDRH review of human factors study
author = Quynh Nhu Nquyen

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

Date: April 30, 2014

To: Julie Golden, MD, CDER/OND/ODEII/DMEP, WO 22, Room 3354,
julie.golden@fda.hhs.gov

Patricia Madara, CDER/OND/ODEIII/DDDP, WO 22, Room 3360,
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James Smith, MD, CDER/OND/ODEII/DMEP, WO 22, Room 3372,
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Office of combination products at combination@fda.gov

Through: Francisco Vicenty, Acting Chief, CDRH/OC/DMQ/REGO, WO-66,
Room 3572

Francisco Vicenty -S
2014.04.30 23:49:45 -04'00'

From: LCDR John W. Diehl, Regulatory Operations Officer,
CDRH/OC/DMQ/REGO, WO-66, Room 3528

Applicant: Novo Nordisk
800 Scudders Mill Road
Plainsboro, New Jersey 08536
FEI: 3010446981

Manufacturer:
Novo Nordisk A/S
Brennum Park
DK-3400 Hillerod
Denmark
FEI: 3003131673

Manufacturer:
Novo Nordisk Pharmaceutical Industry, Inc.
3612 Powhatan Road
Clayton, North Carolina 27520
FEI: 1000158576

Application # NDA 206321

Product Name: Liraglutide injection

Consult Instructions: Request to review firm's response to two deficiencies included in the March 4, 2014 "74-day letter" sent by CDER.

The Office of Compliance at CDRH received a consult request from CDER/OND/ODEIII/DDDP to evaluate NDA 206321 and determine if the firm's March 21, 2014, response to a "74 day letter" was adequate, and whether or not an inspection of any of the firm's facilities would be needed prior to NDA approval.

Liraglutide injection is intended for use in weight loss and maintenance, as an adjunct to diet and exercise, for the treatment of overweight patients with BMI's greater than or equal to 27 kg/m² with co-morbidities, or for the treatment of obese patients with a BMI great than or equal to 30 kg/ m². This product is intended for subcutaneous injection.

Through NDA 206321, Novo Nordisk is requesting approval that the drug substance, Liraglutide 6.0 mg/mL, 3 mL cartridge for use in weight management, be administered subcutaneously to patient. The PDS290 pre-filled pen injector will be the delivery vehicle for the drug substance. The PDS290 pen-injector for liraglutide is capable of delivering does of liraglutide of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg

The PDS290 liraglutide 3.0 mg pen-injector (PDS290) is a prefilled multidose disposable delivery device. The device contains the drug product in a sealed 3 ml cartridge. The technology of the PDS290 is based on the FlexTouch pen-injector.

(b) (4)

Figure 1: PDS 290



Figure 2: Components of the PDS 290

Application documents evaluation

In a February 5, 2014, intercenter consult memorandum (attached), CDRH/OC communicated to CDER/OND/ODEIII/DDDP deficiencies found during the initial review of NDA 206321. CDER then communicated those deficiencies to the firm in a March 4, 2014, information request ("74 day letter"). The firm provided a response to this information request on March 21, 2014.

For ease of review, the deficiencies cited by CDRH/OC in its February 5, 2014, review will be provided below. Under each of the deficiencies will be a review of the firm's response.

1. *Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>*

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

regulations (i.e., Design Controls, Purchasing Controls and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at

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

The firm's response to this deficiency appears to be adequate. In its response, the firm listed the procedures that it follows for Design Controls, Purchasing Controls, and Corrective and Preventive Action, and indicated that these procedures could be made available for review, upon request. On March 26, 2014, CDER requested that the firm provide these procedures for review. On April 3, 2014, these procedures were provided.

- A. With regards to Design Controls, the firm provided the following:
- Medical Device Project Manual;
 - Requirements Engineering for Medical Devices procedure;
 - Design Reviews in medical device development projects procedure;
 - Design Verification of Medical Devices procedure;
 - Design Validation of Medical Devices procedure;
 - Quality Frame Specifications and Defect Classifications for Prefilled Devices procedure;
 - Writing instruction and use of Device Master Record procedure;
 - Change Control procedure; and
 - Configuration Management of Device Development Documents.

The documents provided by the firm were reviewed for compliance with 21 CFR 820.30, and no issues were noted.

- B. With regards to Purchasing Controls, the firm provided the following procedures:
- Selection, Approval and Discontinuation of Direct Spend Suppliers;
 - Re-evaluation of Suppliers-Direct Spend, and
 - Sourcing-Direct Spend.

These documents provided by the firm were reviewed for compliance with 21 CFR 820.50, and no issues were noted.

- C. With regards to Corrective and Preventive Action, the firm provided the following procedures:
- CAPA System; and
 - Corrective and Preventive Action.

These documents provided by the firm were reviewed for compliance with 21 CFR 820.100, and no issues were noted.

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

The firm's response to this deficiency appears to be adequate. The firm provided the list of facilities that perform the manufacturing functions for the PDS290, assemble the PDS290, and add drug substance to the PDS290. Additionally, within the response, the firm provided the name of its facility (Hillerod, Denmark) that maintains the records for Design Controls, Corrective and Preventive Action (CAPA), and Purchasing Controls.

Regulatory history evaluation

After reviewing the application, the following facilities were potentially identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Novo Nordisk
800 Scudders Mill Road

Plainsboro, New Jersey 08536

FEI: 3010446981

Role: Applicant

The facility has no FDA inspectional history. Because all of the records for Design Controls, CAPA, and Purchasing Controls are maintained at the firm's facility in Hillerod, Denmark, it is not recommended that this facility be inspected prior to approval of NDA 206321.

2. Novo Nordisk A/S

Brennum Park

DK-3400 Hillerod

Denmark

FEI: 3003131673

Role: Manufacture of components for PDS290, Final assembly of PDS290, packaging of drug-device combination product, design specification developer, and it is the facility that maintains the records for Design Controls, Purchasing Controls, and CAPA.

An analysis of the firm's FDA inspectional history over the past 2 years showed that an FDA inspection pertaining to medical devices has not been conducted. However, it should be noted that a biologic led inspection was conducted from April 3-12, 2013. This inspection was classified by CBER as VAI. Based on the information provided by the firm in its March 21, 2014, it appears that this facility manufactures the components for PDS290, performs Final assembly of the PDS290, packages the drug-device combination product, and is the facility where the design specifications are developed. Also, this is the facility that maintains the records for Design Controls, Purchasing Controls, and CAPA. Due to the types of activities performed at this facility, and its lack of inspectional history with regards to medical devices, it is recommended that this facility be inspected prior to approval of NDA 206321.

3. Novo Nordisk Pharmaceutical Industry, Inc.

3612 Powhatan Road

Clayton, North Carolina 27520

FEI: 1000158576

Role: Assembly, labelling and packaging of finished drug product

An analysis of this facilities history over the past 2 years showed that an FDA inspection pertaining to medical devices has not been conducted. However, it should be noted that a drug /cGMP drug inspection was conducted from August 13-16, 2012. Because all of the records for Design Controls, CAPA, and Purchasing Controls are maintained at the firm's facility in Hillerod, Denmark, it is not recommended that this facility be inspected prior to approval of NDA 206321.

Deficiencies to be conveyed to the applicant

Michelle Thompson

Senior Director, Regulatory Affairs

Novo Nordisk Inc.

P.O. Box 846

Plainsboro, New Jersey 08536

T: (609) 987-5972

F: (609) 987-3916

EM: mtho@novonordisk.com

No deficiencies were identified during a review of the firm's March 21, 2014, response to FDA's March 4, 2014, "74-Day" letter.

Recommendation

CDRH/OC has completed the evaluation of application NDA 206321, and recommends that the firm's facility in Hillerod, Denmark, be inspected prior to approval.

john.diehl@Digitally signed by
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Date: 2014.05.01 09:29:09 -0400

LCDR John W. Diehl

Appears this way on original

Inspectional guidance

Facility to be inspected:

Novo Nordisk A/S

Brennum Park

DK-3400 Hillerod

Denmark

FEI: 3003131673

Role: Manufacture of components for PDS290, Final assembly of PDS290, packaging of drug-device combination product, design specification developer, and it is the facility that maintains the records for Design Controls, Purchasing Controls, and CAPA.

CDRH recommends the inspection under the applicable Medical Device Regulations of Novo Nordisk A/S, located in Hillerod, Denmark (FEI # 3003131673).

A comprehensive baseline Level 2 inspection focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Liraglutide injection (NDA206321) should be performed.

Additionally, please evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Also, evaluate if and/or how the firm controls other facilities within Novo Nordisk (e.g., Novo Nordisk Pharmaceutical Industry, Inc., Clayton, North Carolina). Detailed inspection guidance can be provided upon request.

Prepared: JDiehl: 4/30/14

Reviewed: FVicenty:4/30/14

CTS No.: ICC1400186

NDA 206321

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

/s/

PATRICIA J MADARA

09/28/2014

Signing for John Diehl, reviewer of manufacturing in CDRH

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 2, 2014

TO: Julie Golden, M. D., Clinical Reviewer
James P. Smith, M.D., M.S., Team Leader
Patricia Madara, Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206321

APPLICANT: Novo Nordisk Inc.

DRUG: Liraglutide

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Weight loss in patients with BMI ≥ 27 kg/m² with co-morbidities, or for

the treatment of obese patients with a BMI ≥ 30 kg/m²

CONSULTATION REQUEST DATE: February 12, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: August 29, 2014

DIVISION ACTION GOAL DATE: October 20, 2014

PDUFA DATE: October 20, 2014

I. BACKGROUND

Novo Nordisk is seeking approval for liraglutide 3.0 mg for weight management. Inspections were requested for three studies:

- **NN8022-1922** “Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes – A 56 week randomized, double-blind, placebo-controlled, three armed parallel group, multi-center, multinational trial with a 12 week observational follow-up period”

The trial was conducted at 126 sites in 9 countries. There were 1351 subjects screened and 846 subjects enrolled. The first subject was enrolled June 1, 2011 and the last subject completed January 25, 2013.

The primary endpoint consisted of 3 co-primary endpoint measures:

- Change from baseline in body weight (fasting body weight) at 56 weeks
 - Proportion of subjects losing at least 5% of baseline body weight at 56 weeks
 - Proportion of subjects losing more than 10% of baseline body weight at 56 weeks
- **NN8022-1923** “Effect of liraglutide on long-term weight maintenance and additional weight loss induced by a 4 to 12 week low calorie diet in obese subjects; A 56 week randomized, double-blind, placebo controlled, parallel group, multi-center trial with a 12 week follow-up period”

The trial was conducted at 26 sites in the US and 10 sites in Canada. There were 675 subjects screened and 422 enrolled. The first subject enrolled October 30, 2008 and the last subject completed September 1, 2010.

There were three co-primary endpoints:

- Fasting body weight loss in %
 - Percentage of subjects who maintain run-in fasting weight loss after 56 weeks of treatment. (Subjects who have a weight regain less than or equal to 0.5% of weight from Week 0 will be regarded as maintenance of run-in fasting weight loss.)
 - Proportion of subjects who lose at least 5% of baseline body weight after 56 weeks on treatment
- **NN8022-1839** “Effect of liraglutide on body weight in non-diabetic obese subjects or overweight subjects with comorbidities: A randomized, double-blind, placebo

controlled parallel group, multi-center, multinational trial with stratification of subjects to either 56 or 160 weeks of treatment based on pre-diabetes status at randomization”

The trial was conducted at 191 sites in 27 countries. In total, 4992 subjects were screened and 3731 subjects were enrolled. The first subject signed the informed consent on June 1, 2001 and the last subject completed March 18, 2013.

The primary efficacy parameters in this trial were change in fasting body weight from baseline to week 56 and the proportion of subjects that lost $\geq 5\%$ and $>10\%$ of baseline fasting body weight at week 56.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 206321 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Harold Bays Site #11519/939	NN8022-1922 10 subjects	5/22-29/2014	NAI
Bret Wittmer Site #11161/126	NN8022-1923 16 subjects	6/23-27/2014	NAI
Mark Fredrick Site #2816/428	NN8022-1839 25 subjects	6/06-26/2014	VAI
Robert Orr Site #44642/965 Site #14544/118	NN8022-1922 6 subjects NN8022-1923 20 subjects	6/19-25/2014	NAI
Joseph Soufer Site #11157/481	NN8022-1839 28 subjects	6/9-24/2014	VAI
Aletha Veenendaal Site # Site 11241/251	NN8022-1839 47 subjects	5/19-27/2014	NAI
Novo Nordisk	NN8022-1922 NN8022-1923 NN8022-1839	6/03-19/2014	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Harold E. Bays, M.D.
3288 Illinois Avenue
Louisville, KY 40213

- a. **What was inspected:** The inspection included review of correspondences with the IRB and sponsor, study monitoring logs, training records, delegation logs, informed consent forms, drug accountability, financial disclosure, 1572s, adverse events, and concomitant medications. There were 10 subject records reviewed.

- b. **General observations/commentary:** This was a well-run, organized site. There were 12 subjects screened and 10 subjects randomized. There was one subject who was a screen failure (Subject 939001) rescreened at a later date and who then became an active subject, 939011.

All subjects signed the informed consent form (ICF) prior to initiation of any study procedures. All used the correct version of the ICF and were updated to any new versions of the ICF. The protocol and all forms of advertising were approved by the institutional review board (IRB) prior to initiation of the study.

There were protocol deviations that were reported and discussed with the sponsor. There were no other protocol deviations noted that were not already reported. All reported adverse events (AE) were properly recorded and there was no under-reporting of AE at this site. The site reported any possible event that could be correlated with the use of the study article based on the definition of an AE found in the protocol, i.e. mosquito bites, so this gave the appearance that they over-reported. Recording of concomitant drugs was also accurate. All data was verifiable in the data listings with no discrepancies. The fasting body weight of all 10 subjects were reviewed in the source data and verified with the values in FDA data listings.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the

submitted data.

2. Bret Alan Wittmer, D.V.M., M.D.*

240 East Ayr Parkway
Madisonville, KY 42431

*All correspondences should be addressed to his widow, Carolyn Wittmer.

- a. **What was inspected:** This was a chart review only of 1572s, IRB approvals, laboratory certifications, informed consent forms, financial disclosure records, test article accountability monitoring reports, and source records. All 16 enrolled subject charts were reviewed. Dr. Brett Wittmer died (b) (6); however, the study was finished in 2010. The Form FDA 482 was issued to his widow. She has taken over responsibility of running the clinic and runs a pediatric service there using nurse practitioners. Since there is no medical physician on site, studies are no longer run from this site. No one from the original study was available for questioning since they are no longer employed by this clinic. Mrs. Wittmer was not involved in the studies.
- b. **General observations/commentary:** There were 21 subjects screened and 16 subjects enrolled. The site used the central IRB (b) (4). All subjects signed the ICF prior to initiating any study procedures. All inclusion/exclusion criteria were verifiable on all active subjects and those who were screen failures. The records were a bit disorganized since this site did not use the sponsor supplied binders to organize the records. There were medical records obtained from other facilities prior to being enrolled into the study that were reviewed. There were no missed concomitant drugs or missed past medical history. The refrigerator temperature records were reviewed and there were no excursions noted.

There were not a lot of reported AEs at this site. The records did not include written notes from office visits so it was hard to find other AEs not reported. The worksheets were the source documents that were supplied by the sponsor. Each office visit had a sheet with a list of questions to ask the subject at each visit. The sheet included a check off box to indicate that the question has been covered. All of the visits had a section with questions about any additional AE. All the boxes were checked. There was a blank sheet available for additional notes, but most of the sheets were left blank or did not offer any information about additional AE. The 10 active subjects were able to maintain the fasting weight loss after 52 weeks. All weight values found in the data listing were verifiable in the source documents. The study was well monitored by the sponsor and any issues were resolved before the site was closed.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.
3. Mark J. Fredrick, M.D., Ph.D
Healthcare Partners Medical Group
19066 Magnolia St.
Huntington Beach, CA 92646
- a. **What was inspected:** Records reviewed included IRB approvals, informed consent forms, 1572s, training, medical history, delegation of duties, laboratory reports, electrocardiogram reports, randomization confirmation, concomitant medications, progress notes, PRO questionnaires, mental health questionnaires, counseling notes, adverse events, discontinuations, and monitoring logs. Primary efficacy data and some secondary efficacy data were verified with data listings. Twenty-six subject records were reviewed.
- b. **General observations/commentary:** Thirty-two subjects were screened, 25 subjects were enrolled, six subjects completed the study, and four subjects were still active in the pre-diabetic extension at the time of the inspection. The first subject signed the informed consent on 6/10/2011 and the last follow-up for a completed subject was 2/28/2013. Of note, the site's informed consent forms did not correspond to the version numbers or dates submitted with the application because reportedly the IRB determines the version numbers of the ICFs.

Dr. Fredrick or the physician sub-investigators signed and dated all patient charts, worksheets, informed consent forms, lab reports, and other source documents used in the study. All original records were on paper. Source documents were complete and legible. Some of the lab reports and other records were found to be misfiled (e.g., Visit 3 lab reports misfiled under Visit 12). Weight was not usually documented to the nearest 0.1 lb as required by the sponsor as a digital scale was not used. Progress notes described multiple attempts made to contact withdrawn subjects for scheduling Early Termination procedures, including several phone calls and certified mail.

The primary efficacy endpoints of subject fasting body weight was compared at randomization and at Visit 17 to data listings for all 25 enrolled subjects and no discrepancies were found. The secondary efficacy endpoints of waist circumference and HbA1c were compared at randomization and Visit 17/End of Treatment (EOT) to data listings for 14 enrolled subjects (where applicable); no discrepancies were found. Concomitant medication and adverse events were compared to data listings for 22 subjects, and discrepancies in concomitant medications were found. The site did not enter protocol deviation data into the electronic database.

For Study NN8022-1923, there were two events noted related to temperature excursions. The first excursion happened with the shipment on November 13, 2008. The site quarantined all affected product and it was destroyed without any dispensing. The second excursion happened with the shipment on June 15, 2009. The product was quarantined and no subject were dispensed the affected product.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted electronically for review. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

5. Joseph Soufer, M.D.
Chase Medical Research LLC
500 Chase Parkway
3rd Floor
Waterbury, CT 06708

- a. What was inspected:** Review of all 28 subject records included comparison of source documents to data listings for primary and secondary efficacy and safety data, inclusion/exclusion criteria, randomization and blinding of subjects, and the screening process. The site was chosen to replace a Russian site that was initially intended for inspection.
- b. General observations/commentary:** There were 34 subjects screened and 28 randomized. All subject records contained an IRB-approved version of the informed consent document which was signed and dated before the subject participated in the research. There was no under-reporting of adverse events. The primary efficacy endpoint data was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.
 - o Females of childbearing potential were to have a serum pregnancy test (hCG) performed in connection with Screening Visit 1 and the End of Treatment visit (Visit 17, 21a or 43b). A serum pregnancy test was not performed at Visit 17 for 7/10 subjects who met this requirement and 2/10 subjects at Visit 21A. There were no known reported pregnancies in these subjects.

- A repeat oral glucose tolerance test was not performed on one subject (481005) who had a fasting plasma glucose that exceeded 200 mg/dL
2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation
- The source document and case report form did not match for one adverse event (upper left quadrant pain vs. intermittent upper right quadrant pain) reported for one subject (481029)

Dr. Soufer responded to the observations in a letter dated July 1, 2014. Corrective actions have been made and the response is acceptable.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

6. Aletha Veenendaal, M.D.
Louis Armstrongweg 78
Almere, NA 1311RL
The Netherlands

- a. What was inspected:** Review was made of 100% of all screened and enrolled ICF forms. All 47 enrolled subjects' charts were reviewed for adverse events and primary efficacy data.
- b. General observations/commentary:** There were 63 subjects screened at the site and 47 subjects enrolled. Thirty-eight subjects completed 56 weeks and 27 subjects continued in a 3-month off-drug observational period. All prospective and enrolled subjects signed the correct versions of the ICF. All protocol deviations and adverse events were reported to the sponsor and IRB. There was no under-reporting of adverse events and the primary efficacy data was verifiable.

One issue addressed during the study concerned unblinding of Subject 0024 pharmacokinetic (PK) results. Dr. Veenendaal inadvertently received from the central laboratory a fax report for PK results which she reviewed. Due to this unblinding incident, Dr. Veenendaal stopped treatment for Subject 0024 and the sub-investigators took over the subject treatment. The Sponsor and IRB were notified.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

7. Novo Nordisk Inc.
1100 Campus Road
Plainsboro, NJ 08540-6650*

*Regulatory correspondence should be addressed to Mr. Robert B. Clark, Vice-President Regulatory Affairs, Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536

- a. **What was inspected:** This inspection covered sponsor/monitor practices related to clinical trials NN8022-1922, NN8022-1923 and NN8022-1839. Regulatory documents for all sites inspected were reviewed. Documentation was reviewed during this inspection for organization and personnel including review of written agreements with contract research organizations, registration of studies on ClinicalTrials.gov, selection and monitoring of clinical investigators including agreements, non-compliance, and training (including protocol specific and GCP training), selection of monitors, monitoring procedures, Quality Assurance (QA) including the audit plan and QA audits, safety and adverse event reporting (including 100% of all SAEs reported), data collection and handling including Standard Operating Procedures (SOPs), financial disclosure, 1572s, electronic records including transmission of data and system security, and test article integrity and accountability. Monitoring activities were reviewed for 10 out of 106 US/Canadian clinical trial sites for Study NN8022-1922 and one site in France (101); 10 out of 26 US/Canadian clinical trial sites for Study NN8022-1923; and 10 out of 69 US/Canadian clinical trial sites and one Russian site (336) for Study NN8022-1839.

- b. **General observations/commentary:** The firm only maintained the original documents for the US and Canadian clinical sites at the inspected location. All files for all other rest-of-the-world clinical sites are maintained at the corporate headquarters in Copenhagen, Denmark. These records were available electronically for review.

The sponsor utilized a number of contract research organizations for the management of the clinical trials. The sponsor utilized the services of the central IRB [REDACTED] (b) (4). The study drug was shipped from Denmark, where it is manufactured. It was packaged, labeled and distributed in the United States. Occasional gaps in monitoring exceeded eight weeks.

Of note, updated financial disclosure forms were not routinely collected by the sponsor. Novo Nordisk considers this an obligation of the investigators to send any changes and updates to disclosure.

One late SUSAR report was noted. This was for Study NN8022-1923, Site #295, Subject 295014. The delay of eight months for reporting was due to a change in the sponsor's causality assessment.

The sponsor did not provide the investigators or the clinical sites with dedicated calibrated scales, or scales of uniform manufacture. Subjects' body weight was measured with a scale in each clinical investigator's office.

During the inspection, Novo Nordisk's drug accountability procedures were discussed. The IWRS (b)(4) Module ((b)(4)) was used. Accountability of destruction of product was not done in IWRS. Drug was either destroyed at the clinical site or sent to a vendor for destruction. When the product was sent to the vendor, there was no final reconciliation of the number of pens received for destruction by anyone within the sponsor's organization. An amended procedure to accomplish this will be implemented in 2015. Novo Nordisk followed up with a written response to this discussion item.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this sponsor appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic clinical sites and one foreign clinical site as well as the sponsor.

Observations noted above for Drs. Wittmer, Fredrick, Orr, and the sponsor are based on the preliminary review of the Establishment Inspection Reports (EIRs). Observations noted above for Drs. Bays and Veenendaal are based on communications from the field investigator. Observations noted above for Dr. Soufer are based on communications from the field investigator and review of the Form FDA-483. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

Two clinical sites inspected, Drs. Fredrick and Soufer, were each issued a Form FDA-483, citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described

above for both sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application.

Drs. Bays, Wittmer, Orr and Veenendaal and the sponsor were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites and the sponsor are considered reliable based on the available information.

In general, based on the inspections of the six clinical sites and the sponsor, the inspectional findings of these sites support validity of data as reported by the sponsor under this NDA.

{See appended electronic signature page}

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Clinical Trials

Date: August 14, 2014

Reviewer: Christian Hampp, PhD
Division of Epidemiology I

Team Leader: Diane K. Wysowski, PhD, MPH
Division of Epidemiology I

Deputy Division Director:
(Acting) David Shih, MD, MS
Division of Epidemiology I

Drug Name: liraglutide (Saxenda, Victoza)

Subject: Analysis of cancers observed in clinical trials of liraglutide
- revised

Application Type/Number: NDA 206321 (Saxenda), NDA 22341 (Victoza)

Applicant/sponsor: Novo Nordisk, Inc.

OSE RCM #: 2014-1200

TSI #: 894 (thyroid tumors with GLP-1 analogs)

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EXECUTIVE SUMMARY

This Division of Epidemiology-I review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

On July 9, 2014, the sponsor provided age-, sex-, trial-, and exposure-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. Follow-up was calculated according to the intent-to-treat principle with a preference given to liraglutide, that is, any person-time after first liraglutide exposure was categorized as exposed to liraglutide, even in the case of re-randomization to a comparator arm in a second study phase. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013, and grouped the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor split the weight management pool into two to reflect that only four of the five trials in that pool included adjudication for cancer outcomes. Cancer outcomes were not adjudicated in the trials included in the diabetes pools.

For internal comparisons, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method, separately for each trial pool. I further calculated RR_{MH} and RD_{MH} for all reported cancer types using only adjudicated malignant events in the weight management pool and non-adjudicated malignant and unspecified events in all liraglutide trial pools.

For external comparisons, I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. I calculated sex- and exposure-specific standardized incidence ratios, which summarize observed vs. expected event counts using age- and sex-standardization.

Clinical trial data with event adjudication in the weight management pool suggest the possibility of increased rates of thyroid cancer (RR_{MH} , 1.90; 95% CI, 0.27-13.35) and female breast cancer not including *in situ* (RR_{MH} , 2.98; 95% CI, 0.69-12.81) among patients exposed to liraglutide compared with patients in comparison arms. However, these associations did not reach statistical significance. Furthermore, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers to the same extent. Limitations suggest that comparisons between clinical trial data and an external reference population be interpreted with caution.

Section 6 of this review contains recommendations to DMEP.

1 INTRODUCTION

This Division of Epidemiology-I (DEPI-I) review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

1.1 BACKGROUND

During the review of clinical trial data for liraglutide in its proposed indication as a weight-loss agent, staff of DMEP noted numeric imbalances in breast cancer and colorectal (benign) and thyroid neoplasms (malignant and benign) compared to placebo. In addition, pooled data from the liraglutide diabetes program demonstrated imbalances in thyroid and breast cancers. DMEP consulted DEPI-I for background incidence rates of these neoplasms, DEPI-I's opinion regarding the likelihood of liraglutide contributing to the observed imbalances, and recommendations including, but not limited to, risk management, labeling, monitoring, and post-marketing studies.

1.2 REGULATORY HISTORY

Liraglutide (Victoza, Novo Nordisk, Inc., NDA 22341) was approved on January 25, 2010, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Currently, the FDA is reviewing a New Drug Application for Saxenda (NDA 206321), a higher dose version of liraglutide proposed for use as a weight-loss agent.

In the Integrated Summary of Safety from November 27, 2013, the sponsor calculated rates of selected types of Event Adjudication Committee (EAC) confirmed neoplasms (breast (malignant and *in situ*), colorectal (benign), pancreatic, and thyroid cancer). The sponsor detected imbalances not favoring liraglutide for breast cancer and benign colorectal neoplasms and a slight imbalance for thyroid cancer. The sponsor did not stratify analyses to incorporate variable treatment allocation ratios between clinical trials. Thus, the comparison of pooled data across clinical trials may not have preserved the benefits of randomization.

1.3 PRODUCT LABELING

The labeling for Victoza contains the following boxed warning:

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid

ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

2 REVIEW METHODS AND MATERIALS

This review includes internal and external comparisons of malignancies observed in various trial pools in the clinical development program of liraglutide.

2.1 DATA REQUEST

On June 20, 2014, FDA requested from the sponsor age-, sex-, and trial-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. The sponsor submitted a proposal on how to address the request on June 23, 2014, which FDA accepted on the same day. The sponsor provided the requested information on July 8, 2014, and a revised version on July 9, 2014. Following another information request on August 12, 2014, the sponsor explained on August 13, 2014, that the July 9, 2014, response inadvertently omitted one event each of colorectal carcinoma, bone metastasis, and lung metastasis. These events occurred in comparator patients in one of the diabetes trials and were included in the current, revised, analyses.

2.2 CLINICAL TRIAL POOLS

Clinical trials in the liraglutide development program (diabetes and weight management programs) included phase 2 and 3 trials with all doses of liraglutide (0.6, 1.2, 1.8, 2.4, and 3.0 mg) and placebo, orlistat, or antidiabetic drugs as comparators. Only comparator arms with drugs approved by the FDA were included in this analysis, which led to the exclusion of insulin degludec and semaglutide comparator arms. Appendix Table 1 contains an overview of trials in the weight management program.

When computing follow-up times, the sponsor applied the intent-to-treat principle with a preference for liraglutide, that is, all person-time occurring after first exposure was categorized as exposed to liraglutide. In trials that featured re-randomization after a certain period (e.g., after 56 weeks in trial 1839) all person-time for patients originally randomized to liraglutide was attributed to liraglutide, regardless of re-randomization to liraglutide or comparator. Follow-up included time when patients were part of the protocol-defined trial (including extensions and observational follow-up), calculated as time from first drug date until last date/date of last visit/date of last contact, whichever came last. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013.

FDA requested grouping of the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor proposed to split the weight management pool into two (Pools 1a and 1b in Table 1), to reflect that only some of the trials included adjudication for cancer outcomes, as described in Section 2.3. The analyses presented in this document were conducted in the following trial pools:

Table 1. Clinical Trial Pools

Pool	Description	Number of trials
1a	All weight management trials	5
1b	Weight management trials with adjudication of cancer events	4
2	All diabetes trials	25
3	Combination of 1a and 2	30

Appendix Table 2 lists individual trials included in each pool and trial- and exposure-specific cumulative follow-up times.

2.3 STUDY OUTCOMES

Outcomes of interest in this analysis were newly diagnosed malignant neoplasms, specifically, invasive thyroid, colorectal, and female breast cancers, and also *in situ* female breast neoplasms.

An independent external EAC adjudicated neoplasms in four out of five trials in the weight management program (Pool 1b, Trials 1839, 1922, 1923, and 3970, see Appendix Table 2). None of the trials that constituted the liraglutide diabetes program included adjudication of neoplasms. To capture malignancy events in all trial pools, the sponsor conducted pre-defined Medical Dictionary for Regulatory Activities (MedDRA) searches using Preferred Terms within the Standardized MedDRA Query (SMQ) “Malignant or unspecified tumors” (MedDRA version 15.1). The sponsor grouped the individual Preferred Terms included in the SMQ ‘Malignant or unspecified tumors’ into categories similar to those used by the EAC in the weight management development program. These categories included: bladder, breast, colorectal, female reproductive, liver, lymphomas, male reproductive, oral, pancreatic, skin, and thyroid neoplasms. The sponsor further created a “miscellaneous” category for neoplasms that could not easily be classified into one of the above categories. For the presentation of breast neoplasms, the sponsor defined the SMQ “Breast neoplasms, malignant and unspecified,” which included a specific Preferred Term to identify *in situ* cases, as requested by the FDA.

According to the sponsor, the MedDRA-based tables included all reported events, but output based on event adjudication only included index events. In the situation where two or more events were linked by the EAC and one of the events was selected as the index event, only this event was counted.

2.4 STATISTICAL ANALYSES

2.4.1 Internal comparisons – randomized

Separately for each clinical trial pool listed in Table 1, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method.¹ This method represents a stratified analysis that computes

¹ Rothman, K.J., Greenland, S., & Lash, T.L. (2008). *Modern Epidemiology*, 3rd Edition, p273. Philadelphia, PA: Lippincott, Williams & Wilkins.

weighted averages across strata (trials), maintains the benefits of randomization, and accounts for different drug-comparator allocation ratios.

I further calculated RR_{MH} and RD_{MH} for all reported cancers using only adjudicated malignant events in the weight management pool (Pool 1b) and non-adjudicated, MedDRA coded malignant and unspecified events in all liraglutide trials (Pool 3).

Clinical trials with zero events of a cancer of interest were included in calculations of RD_{MH} but not in calculations of RR_{MH} . No continuity corrections were used in any of the calculations. The analyses were conducted using Episheet,² and all calculations of RR_{MH} and 95% confidence intervals were verified in SAS 9.3 using a SAS macro for the analysis of stratified clinical trials data.³

2.4.2 External comparisons – not randomized

I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.⁴ This database provided age- and sex-specific rates of invasive thyroid cancer, invasive female breast cancer not including *in situ*, *in situ* breast neoplasm, and invasive colorectal cancer for the years 2007 through 2011.

For each clinical trial pool listed in Table 1, I calculated sex- and exposure-specific standardized incidence ratios (SIRs) and 95% confidence intervals. SIRs summarize observed vs. expected event counts using age- and sex-standardization, that is, expected clinical trial event counts that would be observed in a sample of the U.S. population with the age- and sex-distribution and cumulative follow-up time of the clinical trials. Statistical significance was assumed when the 95% confidence intervals of the SIRs excluded the null value of 1.0. Calculations of SIRs and 95% confidence intervals were conducted using Open Epi.⁵

3 REVIEW RESULTS

3.1 INTERNAL COMPARISONS

3.1.1 Thyroid Cancer

Across all clinical trials (Table 2, Pool 3), 62 malignant and unspecified thyroid neoplasms (MedDRA) were counted among patients exposed to liraglutide and 10 among

² Rothman K. Episheet: Spreadsheet for the analysis of Epidemiologic Data. www.krothman.org/episheet.xls, accessed July 10, 2014.

³ Honda Y, Macaluso M, Brill I. A SAS Program for the Stratified Analysis of Follow-Up Data. *J Occup Health* 1998; 40: 154-157

⁴ National Cancer Institute. Surveillance, Epidemiology, and End Results, Fast Stats interactive tool. <http://seer.cancer.gov/faststats/selections.php?series=cancer>, accessed July 10, 2014.

⁵ Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3.1. www.OpenEpi.com, updated June 23, 2011, accessed July 10, 2014.

patients in comparator arms, resulting in a statistically significant RR_{MH} of 2.00 (95% CI, 1.02-3.91). In the weight management pool with trials that included adjudication (Pool 1b) 15 and 4 malignant and unspecified events (MedDRA) were counted among patients on liraglutide or comparator, respectively, but only 4 and 1 events, respectively, were positively adjudicated as malignant events. Mantel-Haenszel-adjusted rate ratios were largely consistent across trial pools, but did not reach statistical significance, especially when only positively adjudicated malignant events were analyzed in Pool 1b (RR_{MH} , 1.90; 95% CI, 0.27-13.35). Of note, all 4 adjudicated events among patients exposed to liraglutide were categorized as papillary thyroid carcinoma and the event that occurred in the comparator arm (placebo) was categorized as medullary thyroid carcinoma. Effect estimates were somewhat higher for men compared with women, but only one male thyroid cancer case (exposed to liraglutide) was positively adjudicated.

Table 2. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Thyroid Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	Events, n	16	4	6	0	10	4
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1,821.1
	RR _{MH}	1.95		--		1.28	
	95% CI	0.67-5.71		--		0.41-3.98	
	RD _{MH}	15.51		41.74		6.19	
1b	Events, n	15	4	5	0	10	4
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.86		--		1.28	
	95% CI	0.63-5.45		--		0.41-3.98	
	RD _{MH}	15.28		39.28		6.81	
2	Events, n	46	6	24	3	22	3
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	2.03		2.63		1.70	
	95% CI	0.86-4.78		0.73-9.46		0.51-5.64	
	RD _{MH}	34.44		42.40		28.37	
3	Events, n	62	10	30	3	32	7
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	2.00		3.54		1.48	
	95% CI	1.02-3.91		1.02-12.33		0.65-3.36	
	RD _{MH}	24.01		42.16		13.29	
Adjudicated*							
1b	Events, n	4	1	1	0	3	1
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.90		--		1.51	
	95% CI	0.27-13.35		--		0.20-11.55	
	RD _{MH}	4.50		7.86		3.37	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.1.2 Female Breast Cancer

This section describes two analyses for female breast cancer: breast cancer excluding *in situ* (3.1.2.1) and *in situ* neoplasms (3.1.2.2).

3.1.2.1 Female Breast Cancer (excluding *in situ*)

Mantel-Haenszel rate ratios for female breast neoplasms (excluding *in situ*, Table 3) across the different clinical trial pools ranged from 1.52 (95% CI, 0.17-13.36) in Pool 2 (malignant and unspecified) to 2.98 (95% CI, 0.69-12.81) when only positively adjudicated malignant events in Pool 1b were analyzed. None of the associations reached statistical significance.

Table 3. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Female Breast Neoplasms (excluding *in situ*) Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA*			
1a	Events, n	14	3
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.20	
	95% CI	0.64-7.57	
	RD _{MH}	20.03	
1b	Events, n	13	3
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.07	
	95% CI	0.60-7.15	
	RD _{MH}	19.64	
2	Events, n	9	1
	Pt-years	3,028.3	856.8
	RR _{MH}	1.52	
	95% CI	0.17-13.36	
	RD _{MH}	6.87	
3	Events, n	23	4
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.01	
	95% CI	0.69-5.89	
	RD _{MH}	15.82	
Adjudicated*			
1b	Events, n	12	2
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.98	
	95% CI	0.69-12.81	
	RD _{MH}	24.34	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.1.2.2 Female Breast Neoplasm - *in situ*

Across the different clinical trial pools, Mantel-Haenszel-adjusted rate ratios for *in situ* female breast neoplasm (Table 4) ranged from 1.39 (95% CI, 0.15-13.40) when only positively adjudicated events in Pool 1b were analyzed to 2.09 (95% CI, 0.26-17.03) in Pools 1a, 1b, and 3 (MedDRA). No *in situ* breast neoplasms occurred in the diabetes trials (Pool 2) and none of the associations in other trial pools reached statistical significance.

Table 4. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for *in situ* Female Breast Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	Events, n	4	1
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.08	
1b	Events, n	4	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.69	
2	Events, n	0	0
	Pt-years	3,028.3	856.8
	RR _{MH}	--	
	95% CI	--	
	RD _{MH}	0	
3	Events, n	4	1
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	4.13	
Adjudicated			
1b	Events, n	3	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	1.39	
	95% CI	0.15-13.40	
	RD _{MH}	2.42	

3.1.3 Colorectal Cancer

Across all clinical trials (Table 5, Pool 3), 10 malignant and unspecified colorectal neoplasms (MedDRA) occurred among patients exposed to liraglutide and 3 among patients in comparator arms, resulting in a statistically non-significant RR_{MH} of 1.31 (95% CI, 0.36-4.83). In the weight management pool with trials that included adjudication (Pool 1b) 2 and 0 malignant and unspecified colorectal neoplasms (MedDRA) were counted in patients on liraglutide or comparator, respectively; however, 2 and 1 events, respectively, were positively adjudicated malignant cases. No increased risk was evident in the analysis of positively adjudicated events in Pool 1b (RR_{MH} , 0.82; 95% CI, 0.07-9.90), but the 95% confidence interval was wide.

Table 5. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Colorectal Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	Events, n	2	0	1	0	1	0
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1821.1
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.36		4.92		2.60	
1b	Events, n	2	0	1	0	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1669.2
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.68		5.34		2.86	
2	Events, n	8	3	5	1	3	2
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	1.05		1.91		0.52	
	95% CI	0.27-4.01		0.21-17.36		0.09-2.96	
	RD _{MH}	0.74		8.20		-12.64	
3	Events, n	10	3	6	1	4	2
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	1.31		2.22		0.73	
	95% CI	0.36-4.83		0.25-19.83		0.14-3.71	
	RD _{MH}	2.18		7.01		-2.28	
Adjudicated*							
1b	Events, n	2	1	1	1	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	0.82		0.32		--	
	95% CI	0.07-9.90		0.01-7.62		--	
	RD _{MH}	-0.81		-11.40		2.86	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

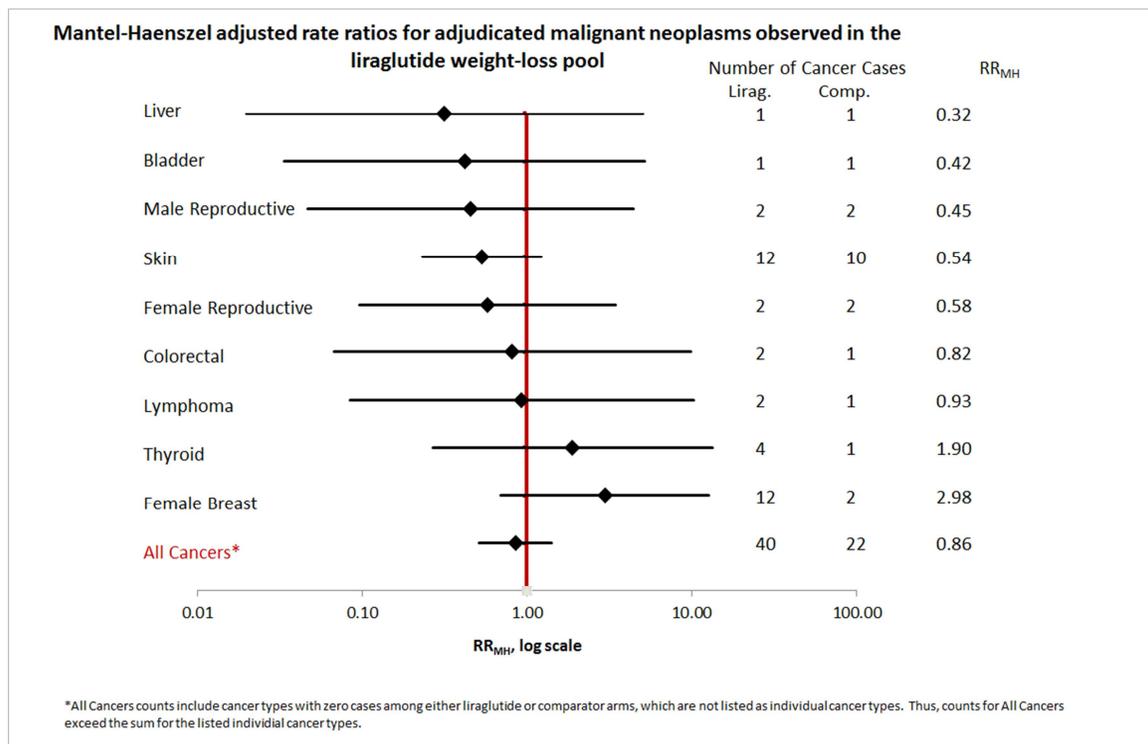
3.1.4 All Cancers

This section summarizes Mantel-Haenszel-adjusted rate ratios by cancer type for all cancers diagnosed in Pool 1b (adjudicated, Section 3.1.4.1) and malignant and unspecified neoplasms in Pool 3 (MedDRA, Section 3.1.4.2).

3.1.4.1 Trial Pool 1b - Adjudicated Malignant Cases

Among all cancer types analyzed in Pool 1b (Figure 1), only thyroid cancer and female breast cancer (excluding *in situ*) occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms. Liraglutide was not associated with an increased risk for all adjudicated malignant cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42), but the 95% confidence interval includes the possibility of a modest increase or decrease in cancer risk. Event counts were small for most cancer types, resulting in wide confidence intervals.

Figure 1. Mantel-Haenszel-Adjusted Rate Ratios for Adjudicated Malignant Neoplasms Observed in the Liraglutide Weight Management Pool

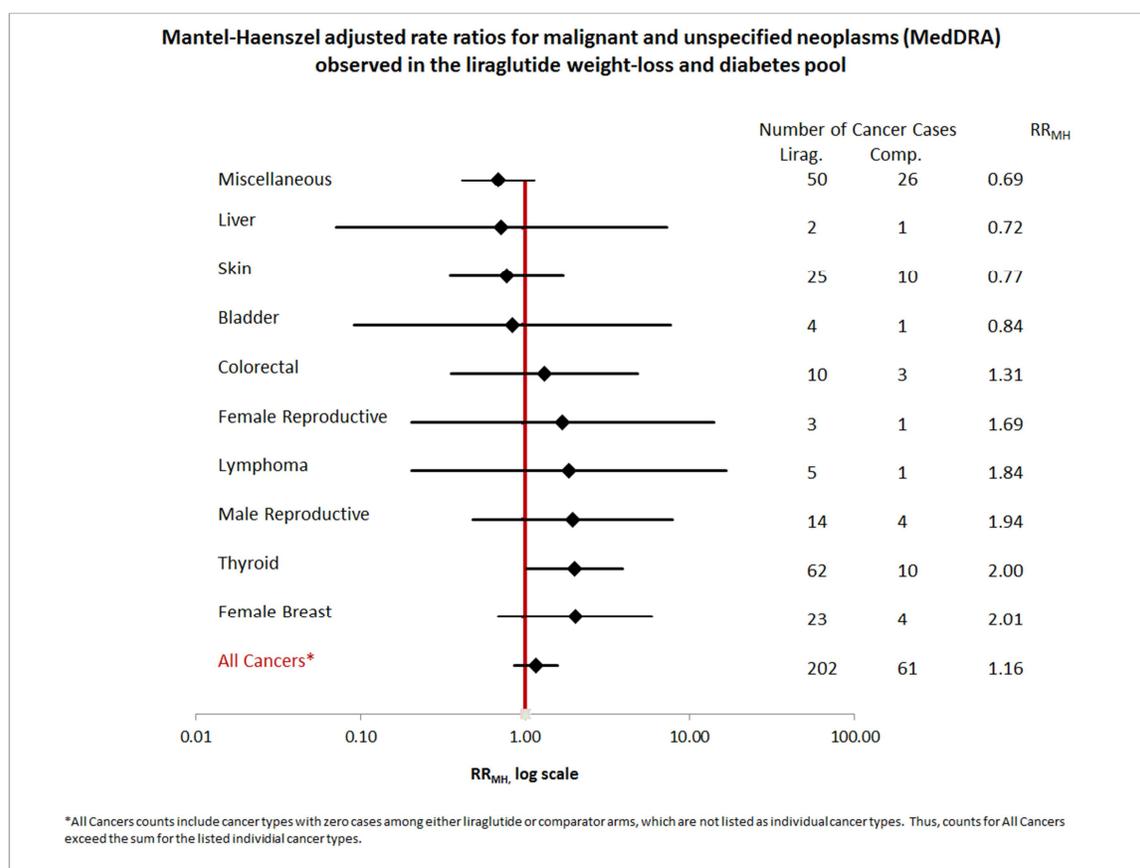


3.1.4.2 Trial Pool 3 – Cases based on MedDRA

Across the liraglutide trials in the weight management and diabetes pool (Pool 3, Figure 2), 202 malignant and unspecified neoplasms were reported among patients exposed to liraglutide and 61 among patients exposed to comparators (RR_{MH} , 1.16; 95% CI, 0.86-1.57). These events were detected using MedDRA coding, without adjudication. Mantel-Haenszel-adjusted rate ratios were elevated for malignant and unspecified neoplasms of the male and female reproductive systems, thyroid, female breast (excluding *in situ*), lymphoma, and colorectal neoplasms. Only the type-specific

association for malignant and unspecified thyroid neoplasm reached statistical significance (RR_{MH} , 2.00; 95% CI, 1.02-3.91).

Figure 2. Mantel-Haenszel-Adjusted Rate Ratios for Malignant and Unspecified Neoplasms (MedDRA) Observed in the Liraglutide Weight Management and Diabetes Pool



3.2 EXTERNAL COMPARISONS

3.2.1 Thyroid Cancer

Across all study pools, regardless of sex, exposure status, or method of ascertainment (MedDRA or EAC adjudication), thyroid neoplasms were more common in the liraglutide clinical trials than what would be expected in the U.S. population with a comparable sex- and age distribution (Table 6). Standardized incidence ratios were highest for males exposed to liraglutide in the diabetes program (SIR, 51.00, 95% CI, 33.43-74.73) where 24 malignant and unspecified MedDRA cases occurred but only 0.47 malignant cases were expected. Smaller counts of EAC-adjudicated malignant thyroid neoplasms in the weight management pool 1b resulted in smaller, but sometimes still statistically significant, SIRs (e.g., liraglutide, both sexes: SIR, 3.43; 95% CI, 1.09-8.27). Standardized incidence ratios were consistently higher among patients exposed to liraglutide compared to patients in comparator arms.

Table 6. Number of Thyroid Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	n(obs.)	16	4	6	0	10	4
	n(exp.)	1.31	0.61	0.16	0.07	1.15	0.54
	SIR	12.24	6.55	38.69	--	8.68	7.36
	95% CI	7.24-19.45	2.08-15.80	15.68-80.46	--	4.41-15.47	2.34-17.75
1b	n(obs.)	15	4	5	0	10	4
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	12.85	7.14	35.43	--	9.75	8.04
	95% CI	7.47-20.73	2.27-17.21	12.98-78.54	--	4.95-17.38	2.55-19.39
2	n(obs.)	46	6	24	3	22	3
	n(exp.)	1.44	0.42	0.47	0.15	0.97	0.28
	SIR	31.91	14.17	51.00	20.29	22.65	10.89
	95% CI	23.63-42.19	5.74-29.47	33.43-74.73	5.16-55.20	14.56-33.74	2.77-29.64
3	n(obs.)	62	10	30	3	32	7
	n(exp.)	2.75	1.03	0.63	0.21	2.12	0.82
	SIR	22.55	9.67	47.94	13.96	15.07	8.54
	95% CI	17.44-28.72	4.91-17.24	32.94-67.58	3.55-37.99	10.48-21.02	3.74-16.90
Adjudicated*							
1b	n(obs.)	4	1	1	0	3	1
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	3.43	1.78	7.09	--	2.92	2.01
	95% CI	1.09-8.27	0.09-8.80	0.35-34.95	--	0.74-7.96	0.10-9.91

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.2.2 Female Breast Cancer

3.2.2.1 Female Breast Cancer (excluding *in situ*)

Female breast neoplasms (excluding *in situ*) occurred somewhat more commonly than expected among women exposed to liraglutide and somewhat less commonly than expected among women in comparator arms. Adjudication of cancer events did not alter these associations. In the weight management pool (Pool 1b), 12 EAC-adjudicated malignant events occurred among women exposed to liraglutide, where 6.23 events would be expected (SIR, 1.92; 95% CI, 1.04-3.27). Two events occurred in the comparator arms, where 3.02 events would be expected (SIR, 0.66; 95% CI, 0.11-2.19). Standardized incidence ratios were somewhat higher in the weight management pools (Pools 1a and 1b), compared with the diabetes pool (Pool 2).

Table 7. Number of Female Breast Neoplasms (not including *in situ*) Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA*			
1a	n(obs.)	14	3
	n(exp.)	6.98	3.27
	SIR	2.01	0.92
	95% CI	1.14-3.29	0.23-2.50
1b	n(obs.)	13	3
	n(exp.)	6.23	3.02
	SIR	2.09	0.99
	95% CI	1.16-3.48	0.25-2.70
2	n(obs.)	9	1
	n(exp.)	8.14	2.39
	SIR	1.11	0.42
	95% CI	0.54-2.03	0.02-2.07
3	n(obs.)	23	4
	n(exp.)	15.12	5.66
	SIR	1.52	0.71
	95% CI	0.99-2.25	0.22-1.71
Adjudicated*			
1b	n(obs.)	12	2
	n(exp.)	6.23	3.02
	SIR	1.92	0.66
	95% CI	1.04-3.27	0.11-2.19

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.2.2.2 Female Breast Neoplasm - *in situ*

In situ female breast neoplasms were not reported during the diabetes program (Pool 2), and were relatively uncommon overall. Regardless, SIRs matched the pattern observed for invasive female breast cancers (Section 3.2.2.1), with modestly higher event counts observed than expected in the weight management pools (Pools 1a and 1b) and somewhat higher SIRs in women exposed to liraglutide compared with women in comparator arms. None of the SIRs reached statistical significance.

Table 8. Number of *in situ* Female Breast Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	n(obs.)	4	1
	n(exp.)	1.99	0.94
	SIR	2.01	1.06
	95% CI	0.64-4.84	0.05-5.25
1b	n(obs.)	4	1
	n(exp.)	1.78	0.87
	SIR	2.25	1.16
	95% CI	0.72-5.43	0.06-5.70
2	n(obs.)	0	0
	n(exp.)	2.25	0.65
	SIR	--	--
	95% CI	--	--
3	n(obs.)	4	1
	n(exp.)	4.24	1.59
	SIR	0.94	0.63
	95% CI	0.30-2.27	0.03-3.10
Adjudicated			
1b	n(obs.)	3	1
	n(exp.)	1.78	0.87
	SIR	1.69	1.16
	95% CI	0.43-4.59	0.06-5.70

3.2.3 Colorectal Cancer

Observed counts of colorectal neoplasms were close to what would be expected in most study pools (Table 9). This was especially notable among EAC-adjudicated malignant events in the weight management pool (Pool 1b), where SIRs among both patients exposed to liraglutide and patients in comparator arms were very close to 1.0. Compared with adjudicated malignant cancers, event counts according to MedDRA (malignant and unspecified neoplasms) and resulting SIRs were slightly higher but none of the SIRs reached statistical significance.

Table 9. Number of Colorectal Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.48	1.10	0.91	0.40	1.50	0.70
	SIR	0.81	--	1.02	--	0.67	--
	95% CI	0.14-2.67	--	0.05-5.04		0.03-3.30	--
1b	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	--	1.10	--	0.74	--
	95% CI	0.15-2.93	--	0.06-5.44		0.04-3.66	--
2	n(obs.)	8	3	5	1	3	2
	n(exp.)	5.65	1.74	3.64	1.14	2.01	0.60
	SIR	1.42	1.72	1.38	0.88	1.49	3.31
	95% CI	0.66-2.69	0.44-4.69	0.50-3.05	0.04-4.34	0.38-4.06	0.56-10.94
3	n(obs.)	10	3	6	1	4	2
	n(exp.)	8.12	2.84	4.61	1.53	3.51	1.31
	SIR	1.23	1.06	1.30	0.65	1.14	1.53
	95% CI	0.63-2.19	0.27-2.88	0.53-2.70	0.03-3.22	0.36-2.75	0.26-5.06
Adjudicated*							
1b	n(obs.)	2	1	1	1	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	0.97	1.10	2.65	0.74	--
	95% CI	0.15-2.93	0.05-4.79	0.06-5.44	0.13-13.08	0.04-3.66	--

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.3 ADJUDICATION

Only Pool 1b contained both malignant and unspecified events detected using MedDRA and malignant events adjudicated by the EAC, which allows for a comparison of these methods. This pool included a total of 62 events confirmed by the EAC as malignant neoplasms and 4 as premalignant breast neoplasms. The sponsor found 12 EAC confirmed malignant neoplasms that were not identified by the SMQ search “Malignant and unspecified tumors.” In contrast, 54 events identified by the SMQ search were reviewed but not confirmed by the EAC as malignant neoplasms. The sponsor listed the following reasons for events not being confirmed as malignancies:

- 34 events were “downgraded” by the EAC; these events were typically reported with unspecific terms such as “neoplasm” or “tumor.”
- 10 events were confirmed either as a pre-malignant (n=7, not including the 4 premalignant breast neoplasms), benign (n=2) or unclassified neoplasm (n=1).
- 2 events were confirmed as a malignant neoplasm, but due to discrepancies between the investigator-reported onset date and that assigned by the EAC, they only appear on the SMQ-based list (as having onset during treatment), and not on the list of EAC-confirmed malignant neoplasms (as the EAC assigned event onset prior to treatment initiation).
- 6 events captured by the SMQ search were confirmed as malignant neoplasms through linking to another EAC-confirmed malignant neoplasm (index event), but only the index event appears on the list of EAC-confirmed malignant neoplasms.
- 1 event was never sent for adjudication and 1 could not be adjudicated due to incomplete source documentation.

Dr. Jonathan Jarow, Medical Officer in the Division of Oncology Drug Products-I, reviewed the sponsor’s external adjudication procedures and found them acceptable.⁶ In fact, they were similar to the methods utilized in the collection of data for the SEER database.

4 DISCUSSION

Analyses presented in this review include internal and external comparisons of neoplasms observed in various trial pools in the clinical development program of liraglutide.

Dr. Jonathan Jarow stated that the best safety population to utilize for describing the risk of cancer in the weight management program includes the adjudicated events from the four weight management trials (Pool 1b in this review).⁶ He further stated that using the larger data set, which also includes the diabetes trials (Pool 3 in this review), has the advantage of increased power, however, at the expense of reliability of event categorization. I agree with his statements. In addition, diabetes trials were of shorter duration (generally 26 weeks) than weight-loss trials (mostly 56 weeks or longer, Appendix Table 1), which makes the detection of a cancer-initiating or -promoting drug effect less likely. It is unfortunate that none of the events in the diabetes program were

⁶ Jonathan P Jarow. OHOP consult on liraglutide. June 24, 2014, available in DARRTS.

adjudicated. As a consequence, the pool with adjudication of malignancies (Pool 1b) included only 4 out of 30 clinical trials in the liraglutide development program, however, with approximately 39.2% of total person-time exposed to liraglutide and 50.8% of total person-time in comparator arms.

As presented in Section 3.1.4.1 and shown in Figure 1, using adjudicated malignant events in Pool 1b, only thyroid cancer and female breast cancer occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms, albeit not statistically significantly. However, liraglutide was not associated with an increased risk of all cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42). In addition, point estimates for individual cancer types ranged from decreased rates for some to increased rates for other cancers. This is not unexpected in a multiple hypothesis testing situation, even in the absence of a treatment effect on the outcome of interest. Nevertheless, although these findings are somewhat reassuring, this analysis cannot exclude the possibility of a causal effect of liraglutide on thyroid cancer or female breast cancer.

With regard to colorectal neoplasm, staff of DMEP observed an imbalance in benign events. However, the scope of this review was limited to malignant or malignant and unspecified events, which were balanced between patients exposed to liraglutide and comparators.

External comparisons showed substantially more new diagnoses of malignant and unspecified thyroid neoplasm (MedDRA) than would be expected based on age- and sex-standardized U.S. population rates, which only include malignant cases. However, for thyroid neoplasm, adjudication rates were low. Of 15 and 4 cases (MedDRA) observed in Pool 1b among patients exposed to liraglutide and comparators, respectively, only 4 and 1 cases, respectively, were positively adjudicated as malignant events. The SIR of adjudicated thyroid cancer events, regardless of exposure status, was much smaller, but in the case of liraglutide-exposed patients still statistically significant. SIRs for female breast and colorectal cancer showed only modest deviations between observed and expected counts. Given the limitations inherent in external comparisons as listed below, modest deviations between observed and expected counts should be interpreted with caution.

Several considerations should be kept in mind when interpreting the data presented in this review. First, these analyses included all neoplasms diagnosed during follow-up, without consideration of induction times. For cases that were diagnosed shortly after study initiation, a cancer-inducing or even -promoting effect of study treatment may be questionable. I refer to Dr. Jarow's review, which includes additional detail and discussion of the timing of malignant events.⁶ Second, in the calculation of person-time, individual follow-up was not censored at the time of a cancer diagnosis. Ordinarily, the time after diagnosis should not be considered time at risk and, therefore, not be included in the denominators of incidence rate calculations. However, for simplicity and to use consistent denominators in the analyses of different cancer types, all available person-time was used. Because of the relative rarity of the endpoints of interest, including or not including person-time after diagnosis will have little effect on the total person-time and the calculation of incidence rates.

In addition to the aforementioned considerations, comparisons between treatment arms of clinical trials and an external standard (i.e. U.S. SEER data) are subject to inherent limitations. Several factors can bias these comparisons either towards higher or lower rates in clinical trials compared with the external standard and some factors could impact clinical trial rates in either direction.

The following factors could potentially lead to higher rates of neoplasms in the reviewed clinical trials compared with U.S. SEER data:

- Association of diabetes and obesity with increased risk of certain cancer types,⁷ including thyroid cancer,^{8,9} breast cancer,¹⁰ and colorectal cancer^{11,12}
- Surveillance bias due to regularly scheduled follow-up visits
- Detection bias related to labeling of liraglutide for thyroid cancer
- Detection bias due to drug effects (e.g. weight loss can facilitate detection of breast cancer; in fact, SIRs for breast cancer were higher in weight-loss than in diabetes pools)
- Inclusion of non-adjudicated events (MedDRA)
- Inclusion of both malignant and unspecified events in analyses based on MedDRA search terms, while U.S. SEER data only included malignant neoplasms
- Inclusion of MedDRA events that were not limited to index events (i.e. primary cancer)
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

The following factors could potentially lead to lower cancer rates in the reviewed clinical trials compared with U.S. SEER data:

- Voluntary participation can result in the selection of healthier patients with higher socioeconomic status and better access to healthcare and prevention
- Inclusion and exclusion criteria may result in a sample at lower risk for cancer
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

⁷ Renehan AG et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–78.

⁸ Kitahara CM et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of 5 prospective studies. *Cancer Epidemiol Biomarkers Prev.* 2011 March; 20(3): 464–472.

⁹ Meinhold CL et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* 2010; 171:242–252.

¹⁰ DeSantis C et al. Breast cancer statistics, 2013. *CA Cancer J Clin.* 2014 Jan-Feb; 64(1):52-62.

¹¹ Jiang Y et al. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol.* 2011; 26:863–876.

¹² Larsson SC et al. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005; 97 (22): 1679-1687.

Although these factors can bias the results in opposing directions, their relative magnitude is difficult to predict and it would be imprudent to assume that they cancel each other out. As a consequence, SIRs resulting from comparisons with an external standard are subject to systematic error and should be interpreted with caution.

5 CONCLUSION

Internal comparisons based on clinical trial data suggest the possibility of increased rates of thyroid cancer and female breast cancer among patients exposed to liraglutide compared with patients in comparison arms. However, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers to the same extent. However, comparisons between clinical trial data and a reference population should be carefully interpreted.

6 RECOMMENDATIONS

A post-marketing observational study is currently ongoing to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to liraglutide (PMR 1583-6), of which DEPI-I has recently reviewed an interim report and posed questions to the sponsor.¹³ Conduct of a separate study focused on a weight-loss indication may be challenging due to limited ability to detect the indication in electronic healthcare data, despite different doses of the drug and different product names used for diabetes and proposed for weight loss. Should liraglutide be approved for weight loss, I do not recommend a separate observational study for cancer with the use of liraglutide as a weight-loss agent.

A cardiovascular outcomes trial is currently underway for liraglutide in the treatment of diabetes (PMR 1583-9). In it, the FDA required the sponsor to also assess long-term effects of Victoza, including neoplasms. If a separate cardiovascular outcomes trial is being considered for liraglutide as a weight-loss agent, it should include adjudication and analysis of malignant neoplasms.

I recommend that DMEP consider adding the observed clinical trial data imbalances in thyroid and female breast cancer in humans to the labeling of Victoza and Saxenda, together with a description of the uncertainty surrounding these estimates.

Christian Hampp, PhD

¹³ Christian Hampp. Year-3 interim report of observational safety study of liraglutide, PMR 1583-6. June 27, 2014, available in DARRTS.

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APPENDIX

Table 1. Clinical Trials in the Liraglutide Weight Management Program (Table 1-1, Saxenda 120-day Safety Report, April 15, 2014)*

Trial ID Phase	Duration of treatment	Population	Doses (mg) ^a	N ^b (SAS)	Trial design features including follow-up period/ Randomization
<i>Completed trials</i>					
<i>Clinical pharmacology</i>					
3630 Phase 1	5 weeks	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0 or 1.8 mg, Placebo	49 (total)	2-week follow-up/ Two-period balanced 6 sequence incomplete cross-over design with minimum 7 subjects in each treatment sequence
<i>Phase 2 and 3</i>					
1807 Phase 2	20 weeks + 84-week extension	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0, 2.4, 1.8, or 1.2 mg Orlistat 120 mg TID Placebo	564 (total), 98 to placebo, 95 to orlistat, 371 to liraglutide	Weeks 20–52 (single-blind): Subjects continued on their randomized treatment. Weeks 52–104 (open-label): Liraglutide/placebo-treated subjects switched to liraglutide 2.4 mg and then 3.0 mg as sites received Ethics Committee approval. Orlistat-treated subjects continued on orlistat. 2-week follow-up period after trial completion. Randomization: 1:1:1:1:1
1839 Phase 3 56-week (main part of trial)	56 weeks	BMI: ≥30 kg/m ² or ≥27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg, Placebo	3723 (total), 1242 placebo, 2481 liraglutide	Subjects without pre-diabetes at screening: After completion of 56-week treatment period, liraglutide-treated subjects were re-randomized to either continue liraglutide or switched to placebo in the following 12 weeks Placebo-treated subjects continue on placebo. Randomization: 2:1
1922 Phase 3	56 weeks	BMI: ≥27 kg/m ² with T2DM	Liraglutide 3.0, 1.8 mg Placebo	844 (total), 212 placebo, 210 liraglutide 1.8 mg, 422 liraglutide 3.0 mg	12-week observational follow-up period after trial completion. Randomization: 2:1:1

*Trials included in analyses of malignant neoplasms are highlighted in yellow.

Table 1 continued

Trial ID Phase	Duration of treatment	Population	Doses (mg) ^a	N ^b (SAS)	Trial design features including follow-up period/ Randomization
3970 Phase 3	32 weeks	BMI: ≥ 30.0 kg/m ² with moderate or severe OSA. T2DM excluded	Liraglutide 3.0 mg Placebo	355 (total), 179 placebo, 176 liraglutide 3.0 mg	2-week follow-up period after trial completion. Randomization: 1:1
1923 Phase 3	56 weeks	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia and/or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	422 (total) 210 placebo 212 liraglutide 3.0 mg	Maintenance of weight loss (min. 5%) achieved during a 4-12 week run-in using a low-calorie diet. 12-week observational follow-up period after trial completion. Randomization: 1:1
Ongoing trials					
3967 Phase 1 Ongoing	5-6 weeks	BMI: Corresponding to ≥ 30 kg/m ² for adults ^c Age: 12-17 years with Tanner stage 2-5 pubertal development	Liraglutide 3.0 mg Placebo	21 (total)	2-week follow-up Randomization: 2:1
1839-ext Phase 3 (104-week extension ongoing)	3 year: 56 weeks + 104- week	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	1584 (total) 497 placebo 1087 liraglutide 3.0 mg	Subjects with pre-diabetes at screening: Treated for up to 3 years (including the 104-week extension period), followed by a 12-week observational follow-up period.

BMI: body mass index; OSA: obstructive sleep apnea; T2DM: type 2 diabetes mellitus; TID: *ter in die*.

a. Once-daily dose with dose-escalation of liraglutide in weekly steps of 0.6 mg in all weight management trials (starting dose: 0.6 mg). **b.** Number of treated subjects. **c.** BMI corresponding to ≥ 30 kg/m² for adults by international cut-off points² and ≤ 45 kg/m² and $\geq 95^{\text{th}}$ percentile for age and sex

Table 2. Clinical Trials included in the Analyses of Malignant Neoplasms

Trial ID	Liraglutide		Comparator		Trial Pool			
	pts. (n)	p-yrs.	pts. (n)	p-yrs.	1a	1b	2	3
NN1250-3948	87	42.3	0*	0*			X	X
NN2211-1310	135	32.3	55	13.0			X	X
NN2211-1332	13	1.9	13	2.1			X	X
NN2211-1333	21	3.7	12	2.1			X	X
NN2211-1334	180	57.5	46	13			X	X
NN2211-1436	695	337.6	345	159.1			X	X
NN2211-1499	72	8.0	72	8.1			X	X
NN2211-1571	123	33.7	40	9.3			X	X
NN2211-1572	724	1022	363	446.5			X	X
NN2211-1573	497	782.2	248	330.3			X	X
NN2211-1574	355	157.2	175	73.4			X	X
NN2211-1697	230	112.3	346	172.3			X	X
NN2211-1700	268	249.4	132	123.6			X	X
NN2211-1701	176	172.6	88	76.3			X	X
NN2211-1796	697	201.6	231	74.1			X	X
NN2211-1797	421	448.4	232	103.5			X	X
NN2211-1799	16	4.2	33	8.6			X	X
NN2211-1842	987	971.4	0	0			X	X
NN2211-1860	573	550.6	219	182.4			X	X
NN2211-2072	176	41.4	34	8.5			X	X
NN2211-3924	240	233	120	117.8			X	X
NN2211-3925	127	88.3	130	89.8			X	X
NN8022-1807	433	559.4	193	197.4	X			X
NN8022-1839	2,481	3,714.3	1,242	1,730.1	X	X		X
NN8022-1922	632	721.3	212	229	X	X		X
NN8022-1923	212	233.4	210	223.4	X	X		X
NN8022-3970	176	97.2	179	104.4	X	X		X
NN9068-3697	1,237	1071	0*	0*			X	X
NA NN9068-3912	199	96.8	0*	0*			X	X
NN9535-1821	95	27.8	46	14.6			X	X
Total	12,278	12,072.8	5,016	4,512.7				

*comparator groups with insulin degludec or semaglutide not included

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/s/

CHRISTIAN HAMPP

08/18/2014

Signed as primary reviewer and acting TL during Diane Wysowski's absence.

DAVID C SHIH

08/18/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 14, 2014

To: Patricia Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206321
OPDP labeling comments for Saxenda™ (liraglutide [rDNA origin] injection), solution for subcutaneous use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labels for Saxenda™ (liraglutide [rDNA origin] injection), solution for subcutaneous use (Saxenda) submitted for consult on March 10, 2014.

Prescribing Information

OPDP's comments on the proposed draft PI are based on the version sent from Patricia Madara (RPM) on August 8, 2014, and are provided directly on the marked version below.

Carton/Container Labels

We recommend that the storage and handling information be revised for consistency with the HOW SUPPLIED/STORAGE AND HANDLING section of the draft PI.

Medication Guide

OPDP's comments on the proposed draft medication guide will be provided under separate cover in conjunction with Division of Medical Policy Programs (DMPP) at a later date.

Thank you for the opportunity to comment on the proposed draft labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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

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

/s/

KENDRA Y JONES
08/14/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Use Review

Date: August 4, 2014

Reviewer: Justin Mathew, Pharm.D., Drug Use Data Analyst
Division of Epidemiology II (DEPI II)

Acting Team Leader: Rajdeep Gill, Pharm.D.
Division of Epidemiology II (DEPI II)

Acting Deputy Director: Hina Mehta, Pharm.D.,
Division of Epidemiology II (DEPI II)

Drug Name(s): Saxenda (liraglutide)

Application Type/Number: 206321

Applicant/Sponsor: Novo Nordisk INC

OSE RCM #: 2014-1228

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

This review analyzes the drug utilization patterns for liraglutide and comparator products (metformin, exenatide, phentermine-topiramate, and lorcaserin) from year 2010 through 2013 and year-to-date May 2014.

The total number of prescriptions dispensed through the U.S. outpatient retail pharmacies for liraglutide and comparator products increased from approximately 51 million prescriptions in 2010 to 68 million prescriptions in year 2013. Patients who received a dispensed prescription for liraglutide or the comparator products increased from approximately 11 million patients in year 2010 to 13 million patients in year 2013. Metformin accounted for majority of the prescriptions and patients. Liraglutide accounted for the second largest proportion of the utilization data by year 2013 with approximately 3-4% of the total. The top diagnosis associated with liraglutide was “Diabetes Mellitus Uncomplicated.”

1 INTRODUCTION

1.1 BACKGROUND

The Division of Metabolism and Endocrinology Products is currently preparing for an advisory committee meeting on September 11, 2014 to discuss the New Drug Application (NDA-206321) of Saxenda[®] (liraglutide) submitted by Novo Nordisk for the indication of weight management in patients with a BMI >30kg/m². Liraglutide currently is marketed as Victoza[®] for the management of type 2 diabetes at doses of 1.2mg and 1.8mg. If approved, Saxenda[®] would be marketed at a dose of 3mg daily. In preparation for the advisory committee meeting, the Division of Epidemiology II was requested to provide the drug utilization patterns for liraglutide as well as metformin, exenatide (Byetta[®] and Bydureon[®]), phentermine-topiramate (Qsymia[®]), and lorcaserin (Belviq[®]).

1.2 PRODUCT LABELING

Victoza[®] (liraglutide) is a glucagon-like peptide-1 (GLP-1) receptor agonist approved on January 25, 2010. Victoza[®] is currently indicated as:

- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹ The safety and efficacy of liraglutide has not been established in the pediatric population.
- Victoza[®] is available as:
 - **Injectable:** Solution for Subcutaneous Use (18mg/3ml).

Metformin is an oral antihyperglycemic drug originally approved on March 3, 1995 under the brand name Glucophage[®]. It is currently indicated for the treatment of type 2 diabetes as:²

¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s0201bl.pdf

² Metformin: Drug Facts and Comparisons [online]. 2014. St. Louis, MO: Wolters Kluwer Health, Inc; Accessed April 26, 2014 <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12780&quick=500789|5&search=500789|5&isstemmed=True&NDCmapping=-1&fromTop=true#firstMatch>

- **Monotherapy:** As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin immediate-release tablets and solution are indicated in patients 10 years of age and older. Metformin extended-release (ER) tablets are indicated in adults.
- **Combination therapy:** Metformin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults.
- Metformin is available as:
 - **Tablet:** 500mg, 750mg, 850mg, 1,000mg
 - **Oral Solution:** 500mg/5mL

Belviq[®] (lorcaserin) is a 5-HT_{2c} receptor agonist that was approved on June 27, 2012. Belviq[®] is indicated for:³

- **Chronic weight management:** as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese) or 27 kg/m² or greater (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)
- Belviq[®] is available as:
 - **Tablet:** 10mg

Qsymia[®] (phentermine-topiramate extended release) was approved on July 17, 2012 and is indicated for:

- **Chronic weight management:** As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese) or 27 kg/m² or greater (overweight) in the presence of at least 1 weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or dyslipidemia.⁴
- Qsymia[®] (phentermine-topiramate extended-release) is available as:
 - **Tablet:** 3.75mg/23mg, 7.5mg/46mg, 11.25mg/69mg, and 15mg/92mg.

Exenatide is a GLP-1 receptor agonist currently marketed as Byetta[®] and Bydureon[®]. Byetta[®] was originally approved on April 28, 2005 while Bydureon[®] (extended-release formulation) was approved on January 27, 2012. Byetta[®] and Bydureon[®] are indicated for:

- **Type 2 diabetes mellitus:** treatment of type 2 diabetes mellitus, in noninsulin dependent patients, to improve glycemic control as an adjunct to diet and exercise.
- Exenatide is available as:
 - **Injectable:** Subcutaneous Solution
 - **Bydureon[®]:** 2mg
 - **Byetta[®]:** 10MCG/0.04mL and 5MCG/0.02mL

³ Belviq[®]. Drug Facts and Comparisons [online]. 2014. St. Louis, MO: Wolters Kluwer Health, Inc; Accessed July 22, 2014 <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp18601&quick=953590|5&search=953590|5&isstemmed=True&NDCmapping=-1&fromTop=true#firstMatch>

⁴ Qsymia. Drug Facts and Comparisons. Drug Facts and Comparisons [online]. 2014. St. Louis, MO: Wolters Kluwer Health, Inc; Accessed July 22, 2014. < <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp18615&quick=1356769|5&search=1356769|5&isstemmed=True&NDCmapping=-1&fromTop=true#firstMatch>>

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales PerspectiveTM was used to determine the various retail and non-retail channels of distribution for liraglutide. Sales data for year **2013** indicated that liraglutide was primarily distributed to the outpatient retail pharmacy setting (70%) while the mail-order/specialty pharmacy and the non-retail pharmacy settings accounted for 25% and 5% of the total sales, respectively⁵. As a result, only the outpatient retail pharmacy utilization patterns were examined in this review. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Non-retail pharmacy and mail-order/specialty pharmacies settings data were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for liraglutide as well as metformin, exenatide, phentermine-topiramate, and lorcaserin from the U.S. outpatient retail pharmacies for the years 2010 to 2013 and year-to-date May 2014.

The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription for liraglutide, metformin, exenatide, phentermine-topiramate, and lorcaserin from U.S. outpatient retail pharmacies for years 2010 through 2013 and year-to-date May 2014.

Based on office-based physician survey data in the U.S., diagnoses associated with the use of liraglutide were obtained from Encuity Research, LLC., Treatment AnswersTM with Pain Panel, for the cumulative time period from January 2010 through May 2014.

3 RESULTS

3.1 PRESCRIPTION DATA

Table 1 in Appendix 1 provides the nationally estimated number of dispensed prescriptions for liraglutide and comparators (metformin, exenatide, phentermine-topiramate, and lorcaserin) from the U.S. outpatient retail pharmacies from year 2010 through 2013 and year-to-date May 2014. The total number of dispensed prescriptions for the selected five molecules increased from approximately 51 million prescriptions dispensed in year 2010 to approximately 68 million prescriptions dispensed in year 2013. Metformin accounted for 94-96% of the total prescriptions dispensed during the time period examined. Liraglutide initially accounted for approximately 490,000 prescriptions dispensed during year 2010 and increased to approximately 2.3 million prescriptions dispensed in year 2013. Exenatide prescriptions decreased slightly from approximately

⁵ IMS Health, National Prescription Audit (NPA). Years 2010 through 2013 and year-to-date May 2014. Extracted June 2014. File: IMS (NSPC-NPA-TPT) 2014-1228 Saxenda AC June 27.xlsx

1.6 million prescriptions dispensed in 2010 to 1.2 million prescriptions dispensed in year 2013. Phentermine-topiramate (approximately 183,000 prescriptions) and lorcaserin (approximately 106,000 prescriptions), each accounted for less than 1% of the total prescriptions dispensed in year 2013.

3.2 PATIENT DATA

Table 2 in Appendix 1 provides the nationally estimated number of unique patients who received a dispensed prescription for liraglutide and comparators (metformin, exenatide, phentermine-topiramate, and lorcaserin) from the U.S. outpatient retail pharmacies from year 2010 through 2013 and year-to-date May 2014. The total number of patients who received a dispensed prescription for liraglutide and comparators increased from approximately 11 million patients in year 2010 to approximately 13 million patients in year 2013. Throughout the time period examined, patients receiving a prescription for metformin accounted for the largest proportion, ranging from 98% (approximately 11 million patients) of the total patients in year 2010 to 96% (approximately 12.5 million patients) of the total patients in year 2013.

The number of patients who received a dispensed prescription for liraglutide nearly tripled from 178,000 patients in year 2010 to 521,000 patients in 2013. The number of patients receiving a dispensed prescription for exenatide decreased from nearly 377,000 patients in 2010 to nearly 262,000 patients during the study period. Patients receiving phentermine-topiramate and lorcaserin prescriptions each accounted for less than 1% of the total patients with 108,000 patients and 63,000 patients, respectively, during year 2013,

3.3 DIAGNOSES DATA

Table 3 in Appendix 1 shows the diagnoses associated with the use of liraglutide during the cumulative time period from January 2010 through May 2014. Diagnoses expressed in terms of *drug use mentions*⁶ were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates.

There were a total of approximately 4 million diagnoses (95% CI 3,766,000-4,390,000) associated with the use of liraglutide during the examined time period. “Diabetes Mellitus Uncomplicated” (ICD-9 code 250.0) was the top diagnosis associated with the use of liraglutide with a point estimate of 3.9 million uses (95% CI 3,558,000-4,165,000). “Diabetes with Neurologic Manifestations” (ICD-9 code 250.6) followed with 1.8% of the total uses or a point estimate of 72,000 uses (95% CI 30,000-113,000) and “Neuropathy in Diabetes” (ICD-9 code 357.2) with 1.5% of the total uses or a point estimate of 60,000 uses (95% CI 22,000-97,000). The diagnosis of “Obesity” (ICD-9 code 278.0) associated with the use of liraglutide accounted for less than 1% of the total or a point estimate of 34,000 uses (95% CI 5,000-62,000). However, the number of mentions of liraglutide associated with the diagnosis of obesity was below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

⁶ The term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

4 DISCUSSION

The overall findings from this review illustrate that the use of liraglutide has increased during the time period examined. However, among liraglutide and comparator products, metformin accounted for majority of utilization throughout the time period examined. The majority of diagnoses were related to diabetes; the approved indication for liraglutide. The diagnosis of obesity associated with liraglutide accounted for less than 1% of the total drug use mentions.

Although phentermine-topiramate was approved in July 2012, there was an initial restriction of distribution from four certified pharmacies (primarily mail-order). Hence, low utilization data was captured in the outpatient retail setting until April 2013 when a REMS modification allowed for additional certified retail pharmacies to start dispensing this drug.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2013 indicated that the majority of (70% of total sales) liraglutide was distributed to the outpatient retail pharmacy setting. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution.

We focused our analyses on only the outpatient retail pharmacy settings, therefore these estimates may not apply to other settings of care, such as mail-order/specialty pharmacies, clinics, and hospitals, in which these products are used. The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSION

Overall, the use of liraglutide and comparator products increased during the time period examined from nearly 11 million patients and 51 million prescriptions dispensed in year 2010 to 13 million patients and 68 million prescriptions dispensed in year 2013. Liraglutide prescriptions increased over four-fold while the number of patients on liraglutide has nearly tripled from year 2010 through year 2013. The most common diagnosis associated with liraglutide use was “Diabetes Mellitus Uncomplicated” and only a small fraction (less than 1%) of the total diagnoses were associated with “Obesity”.

APPENDIX 1: Tables.

TABLE 1.

Nationally Estimated Number of Dispensed Prescriptions for Liraglutide and Comparators From U.S. Outpatient Retail Pharmacies, Years 2010 Through 2013 and Year-to-Date May 2014										
	2010		2011		2012		2013		YTD May 2014	
	TRx	% Share								
TOTAL	50,956,140	100.0%	52,778,444	100.0%	61,684,285	100.0%	67,851,438	100.0%	29,654,547	100.0%
METFORMIN	48,897,399	96.0%	50,278,640	95.3%	58,623,296	95.0%	64,042,124	94.4%	27,722,314	93.5%
LIRAGLUTIDE	489,668	1.0%	1,249,084	2.4%	1,771,645	2.9%	2,275,015	3.4%	1,042,659	3.5%
EXENATIDE	1,569,073	3.1%	1,250,720	2.4%	1,289,144	2.1%	1,246,051	1.8%	534,850	1.8%
PHEENTERMINE - TOPIRAMATE	--	--	--	--	200	<0.1%	182,558	0.3%	211,727	0.7%
LORCASERIN	--	--	--	--	--	--	105,690	0.2%	142,997	0.5%

IMS Health, National Prescription Audit (NPA). Years 2010 through 2013 and year-to-date May 2014. Extracted June 2014. File: IMS (NSPC-NPA-TPT) 2014-1228 Saxenda AC June 27.xlsx

TABLE 2.

Nationally Estimated Number of Patients Who Received Dispensed Prescription for Liraglutide and Comparators From U.S. Outpatient Retail Pharmacies, Years 2010 Through 2013 and Year-to-Date May 2014										
	2010		2011		2012		2013		YTD May 2014	
	Patient (n)	% Share								
TOTAL	11,195,825	100.0%	11,838,379	100.0%	12,213,414	100.0%	12,937,032	100.0%	10,718,176	100.0%
METFORMIN	10,973,718	98.0%	11,588,710	97.9%	11,929,223	97.7%	12,468,832	96.4%	10,272,459	95.8%
LIRAGLUTIDE	177,875	1.6%	322,381	2.7%	416,207	3.4%	520,589	4.0%	410,152	3.8%
EXENATIDE	376,775	3.4%	297,603	2.5%	287,506	2.4%	262,495	2.0%	190,128	1.8%
PHEENTERMINE - TOPIRAMATE	--	--	--	--	60	<0.1%	108,318	0.8%	107,960	1.0%
LORCASERIN	--	--	--	--	--	--	63,414	0.5%	88,213	0.8%

*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

IMS Health, National Prescription Audit (NPA). Years 2010 through 2013 and year-to-date May 2014. Extracted June 2014. File: IMS (NSPC-NPA-TPT) 2014-1228 Saxenda AC June 27.xlsx

TABLE 3.

Diagnosis Associated With the Use of Liraglutide as Reported by U.S. Office-Based Physician Surveys, January 2010 through May 2014			
	January 2010 - May 2014		
	Uses	95% Confidence Interval	Share %
Liraglutide	4,078,000	3,766,000 - 4,390,000	100.0%
2500 DIABETES MELLITUS UNCOMP	3,861,000	3,558,000 - 4,165,000	94.7%
2506 DIAB W NEUROLOGIC MANIF	72,000	30,000 - 113,000	1.8%
3572 NEUROPATHY IN DIABETES	60,000	22,000 - 97,000	1.5%
2780 OBESITY	34,000	5,000 - 62,000	0.8%
2777 DYSMETABOLIC SYNDROME X	27,000	2,000 - 52,000	0.7%
7902 ABNORMAL GLUCOSE	11,000	<500 - 27,000	0.3%
2509 DIABETES W COMPLIC NOS	7,000	<500 - 20,000	0.2%
7906 ABN BLOOD CHEMISTRY NEC	7,000	<500 - 20,000	0.2%

** Encuity Research LLC., recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence intervals.*

Source: Encuity Research, LLC, Treatment Answers™ with Pain Panel. January 2010 through May 2014. File: Enquity 2014-1228 Saxenda AC July 17.xlsx

APPENDIX 1: Drug Use Database Descriptions.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., TreatmentAnswers with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

JUSTIN A MATHEW
08/04/2014

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drug use data cleared by the data vendors

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Clinical Trials

Date: July 25, 2014

Reviewer: Christian Hampp, PhD
Division of Epidemiology I

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Division of Epidemiology I

Drug Name: liraglutide (Saxenda, Victoza)

Subject: Analysis of cancers observed in clinical trials of liraglutide

Application Type/Number: NDA 206321 (Saxenda), NDA 22341 (Victoza)

Applicant/sponsor: Novo Nordisk, Inc.

OSE RCM #: 2014-1200

TSI #: 894 (thyroid tumors with GLP-1 analogs)

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EXECUTIVE SUMMARY

This Division of Epidemiology-I review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

On July 9, 2014, the sponsor provided age-, sex-, and trial-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. Follow-up was calculated according to the intent-to-treat principle with a preference given to liraglutide, that is, any person-time after first liraglutide exposure was categorized as exposed to liraglutide, even in the case of re-randomization to a comparator arm in a second study phase. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013, and grouped the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor split the weight management pool into two to reflect that only four of the five trials in that pool included adjudication for cancer outcomes. Cancer outcomes were not adjudicated in the trials included in the diabetes pools.

For internal comparisons, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method, separately for each trial pool. I further calculated RR_{MH} and RD_{MH} for all reported cancer types using only adjudicated events in the weight management pool and non-adjudicated events in all liraglutide trial pools.

For external comparisons, I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. I calculated sex- and exposure-specific standardized incidence ratios, which summarize observed vs. expected event counts using age- and sex-standardization.

Clinical trial data with event adjudication in the weight management pool suggest the possibility of increased rates of thyroid cancer (RR_{MH} , 1.90; 95% CI, 0.27-13.35) and female breast cancer not including *in situ* (RR_{MH} , 2.98; 95% CI, 0.69-12.81) among patients exposed to liraglutide compared with patients in comparison arms. However, these associations did not reach statistical significance. Furthermore, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers. Limitations suggest that comparisons between clinical trial data and an external reference population be interpreted with caution.

Section 6 of this review contains recommendations to DMEP.

1 INTRODUCTION

This Division of Epidemiology-I (DEPI-I) review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

1.1 BACKGROUND

During the review of clinical trial data for liraglutide in its proposed indication as a weight-loss agent, staff of DMEP noted numeric imbalances in breast, colorectal (benign), and thyroid neoplasms (malignant and benign) compared to placebo. In addition, pooled data from the liraglutide diabetes program demonstrated imbalances in thyroid and breast cancers. DMEP consulted DEPI-I for background incidence rates of these malignancies, DEPI-I's opinion regarding the likelihood of liraglutide contributing to the observed imbalances, and recommendations including, but not limited to, risk management, labeling, monitoring, and post-marketing studies.

1.2 REGULATORY HISTORY

Liraglutide (Victoza, Novo Nordisk, Inc., NDA 22341) was approved on January 25, 2010, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Currently, the FDA is reviewing a New Drug Application for Saxenda (NDA 206321), a higher dose version of liraglutide proposed for use as a weight-loss agent.

In the Integrated Summary of Safety from November 27, 2013, the sponsor calculated rates of selected types of Event Adjudication Committee (EAC) confirmed neoplasms (breast (malignant and *in situ*), colorectal (benign), pancreatic, and thyroid cancer). The sponsor detected imbalances not favoring liraglutide for breast cancer and benign colorectal neoplasms and a slight imbalance for thyroid cancer. The sponsor did not stratify analyses to incorporate variable treatment allocation ratios between clinical trials. Thus, the comparison of pooled data across clinical trials may not have preserved the benefits of randomization.

1.3 PRODUCT LABELING

The labeling for Victoza contains the following boxed warning:

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid

ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

2 REVIEW METHODS AND MATERIALS

This review includes internal and external comparisons of malignancies observed in various trial pools in the clinical development program of liraglutide.

2.1 DATA REQUEST

On June 20, 2014, FDA requested from the sponsor age-, sex-, and trial-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. The sponsor submitted a proposal on how to address the request on June 23, 2014, which FDA accepted on the same day. The sponsor provided the requested information on July 8, 2014, and a revised version on July 9, 2014.

2.2 CLINICAL TRIAL POOLS

Clinical trials in the liraglutide development program (diabetes and weight management programs) included phase 2 and 3 trials with all doses of liraglutide (0.6, 1.2, 1.8, 2.4, and 3.0 mg) and placebo, orlistat, or antidiabetic drugs as comparators. Only comparator arms with drugs approved by the FDA were included in this analysis, which led to the exclusion of insulin degludec and semaglutide comparator arms. Appendix Table 1 contains an overview of trials in the weight management program.

When computing follow-up times, the sponsor applied the intent-to-treat principle with a preference for liraglutide, that is, all person-time occurring after first exposure was categorized as exposed to liraglutide. In trials that featured re-randomization after a certain period (e.g., after 56 weeks in trial 1839) all person-time for patients originally randomized to liraglutide was attributed to liraglutide, regardless of re-randomization to liraglutide or comparator. Follow-up included time when patients were part of the protocol-defined trial (including extensions and observational follow-up), calculated as time from first drug date until last date/date of last visit/date of last contact, whichever came last. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013.

FDA requested grouping of the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor proposed to split the weight management pool into two (Pools 1a and 1b in Table 1), to reflect that only some of the trials included adjudication for cancer outcomes, as described in Section 2.3. The analyses presented in this document were conducted in the following trial pools:

Table 1. Clinical Trial Pools

Pool	Description	Number of trials
1a	All weight management trials	5

1b	Weight management trials with adjudication of cancer events	4
2	All diabetes trials	25
3	Combination of 1a and 2	30

Appendix Table 2 lists individual trials included in each pool and trial- and exposure-specific cumulative follow-up times.

2.3 STUDY OUTCOMES

Outcomes of interest in this analysis were treatment-emergent malignant neoplasms, specifically, invasive thyroid, colorectal, and female breast cancers, and also *in situ* female breast cancers.

An independent external EAC adjudicated neoplasms in four out of five trials in the weight management program (Pool 1b, Trials 1839, 1922, 1923, and 3970, see Appendix Table 2). None of the trials that constituted the liraglutide diabetes program included adjudication of neoplasms. To capture malignancy events in all trial pools, the sponsor conducted pre-defined Medical Dictionary for Regulatory Activities (MedDRA) searches using Preferred Terms within the Standardized MedDRA Query (SMQ) “Malignant or unspecified tumors” (MedDRA version 15.1). The sponsor grouped the individual Preferred Terms included in the SMQ ‘Malignant or unspecified tumors’ into categories similar to those used by the EAC in the weight management development program. These categories included: bladder, breast, colorectal, female reproductive, liver, lymphomas, male reproductive, oral, pancreatic, skin, and thyroid neoplasms. The sponsor further created a “miscellaneous” category for neoplasms that could not easily be classified into one of the above categories. For the presentation of breast neoplasms, the sponsor defined the SMQ “Breast neoplasms, malignant and unspecified,” which included a specific Preferred Term to identify *in situ* cancers, as requested by the FDA.

According to the sponsor, the MedDRA-based tables included all reported events, but output based on event adjudication only included index events. In the situation where two or more events were linked by the EAC and one of the events was selected as the index event, only this event was counted.

2.4 STATISTICAL ANALYSES

2.4.1 Internal comparisons – randomized

Separately for each clinical trial pool listed in Table 1, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method.¹ This method represents a stratified analysis that computes weighted averages across strata (trials), maintains the benefits of randomization, and accounts for different drug-comparator allocation ratios.

¹ Rothman, K.J., Greenland, S., & Lash, T.L. (2008). *Modern Epidemiology*, 3rd Edition, p273. Philadelphia, PA: Lippincott, Williams & Wilkins.

I further calculated RR_{MH} and RD_{MH} for all reported cancers using only adjudicated events in the weight management pool (Pool 1b) and non-adjudicated, MedDRA coded events in all liraglutide trials (Pool 3).

Clinical trials with zero events of a cancer of interest were included in calculations of RD_{MH} but not in calculations of RR_{MH} . No continuity corrections were used in any of the calculations. The analyses were conducted using Episheet,² and all calculations of RR_{MH} and 95% confidence intervals were verified in SAS 9.3 using a SAS macro for the analysis of stratified clinical trials data.³

2.4.2 External comparisons – not randomized

I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.⁴ This database provided age- and sex-specific rates of invasive thyroid cancer, invasive female breast cancer not including *in situ*, *in situ* female breast cancer, and invasive colorectal cancer for the years 2007 through 2011.

For each clinical trial pool listed in Table 1, I calculated sex- and exposure-specific standardized incidence ratios (SIRs) and 95% confidence intervals. SIRs summarize observed vs. expected event counts using age- and sex-standardization, that is, expected clinical trial event counts that would be observed in a sample of the U.S. population with the age- and sex-distribution and cumulative follow-up time of the clinical trials. Statistical significance was assumed when the 95% confidence intervals of the SIRs excluded the null value of 1.0. Calculations of SIRs and 95% confidence intervals were conducted using Open Epi.⁵

3 REVIEW RESULTS

3.1 INTERNAL COMPARISONS

3.1.1 Thyroid Cancer

Across all clinical trials (Table 2, Pool 3), 62 thyroid cancers (MedDRA) occurred among patients exposed to liraglutide and 10 among patients in comparator arms, resulting in a statistically significant RR_{MH} of 2.00 (95% CI, 1.02-3.91). In the weight management pool with trials that included adjudication (Pool 1b) 15 and 4 events (MedDRA) were

² Rothman K. Episheet: Spreadsheet for the analysis of Epidemiologic Data. www.krothman.org/episheet.xls, accessed July 10, 2014.

³ Honda Y, Macaluso M, Brill I. A SAS Program for the Stratified Analysis of Follow-Up Data. *J Occup Health* 1998; 40: 154-157

⁴ National Cancer Institute. Surveillance, Epidemiology, and End Results, Fast Stats interactive tool. <http://seer.cancer.gov/faststats/selections.php?series=cancer>, accessed July 10, 2014.

⁵ Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3.1. www.OpenEpi.com, updated June 23, 2011, accessed July 10, 2014.

counted among patients on liraglutide or comparator, respectively, but only 4 and 1 events, respectively, were positively adjudicated. Mantel-Haenszel-adjusted rate ratios were largely consistent across trial pools, but did not reach statistical significance, especially when only positively adjudicated events were analyzed in Pool 1b (RR_{MH} , 1.90; 95% CI, 0.27-13.35). Effect estimates were somewhat higher for men compared with women, but only one male thyroid cancer case (exposed to liraglutide) was positively adjudicated.

Table 2. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Thyroid Cancer Cases Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA							
1a	Events, n	16	4	6	0	10	4
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1,821.1
	RR _{MH}	1.95		--		1.28	
	95% CI	0.67-5.71		--		0.41-3.98	
	RD _{MH}	15.51		41.74		6.19	
1b	Events, n	15	4	5	0	10	4
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.86		--		1.28	
	95% CI	0.63-5.45		--		0.41-3.98	
	RD _{MH}	15.28		39.28		6.81	
2	Events, n	46	6	24	3	22	3
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	2.03		2.63		1.70	
	95% CI	0.86-4.78		0.73-9.46		0.51-5.64	
	RD _{MH}	34.44		42.40		28.37	
3	Events, n	62	10	30	3	32	7
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	2.00		3.54		1.48	
	95% CI	1.02-3.91		1.02-12.33		0.65-3.36	
	RD _{MH}	24.01		42.16		13.29	
Adjudicated							
1b	Events, n	4	1	1	0	3	1
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.90		--		1.51	
	95% CI	0.27-13.35		--		0.20-11.55	
	RD _{MH}	4.50		7.86		3.37	

3.1.2 Female Breast Cancer

This section describes two analyses for female breast cancer: invasive cancers (3.1.2.1) and *in situ* breast cancers (3.1.2.2).

3.1.2.1 Female Breast Cancer (excluding *in situ*)

Mantel-Haenszel rate ratios for female breast cancer (excluding *in situ*, Table 3) across the different clinical trial pools ranged from 1.52 (95% CI, 0.17-13.36) in Pool 2 to 2.98 (95% CI, 0.69-12.81) when only positively adjudicated events in Pool 1b were analyzed. None of the associations reached statistical significance.

Table 3. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Female Breast Cancer Cases (excluding *in situ*) Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	Events, n	14	3
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.20	
	95% CI	0.64-7.57	
	RD _{MH}	20.03	
1b	Events, n	13	3
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.07	
	95% CI	0.60-7.15	
	RD _{MH}	19.64	
2	Events, n	9	1
	Pt-years	3,028.3	856.8
	RR _{MH}	1.52	
	95% CI	0.17-13.36	
	RD _{MH}	6.87	
3	Events, n	23	4
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.01	
	95% CI	0.69-5.89	
	RD _{MH}	15.82	
Adjudicated			
1b	Events, n	12	2
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.98	
	95% CI	0.69-12.81	
	RD _{MH}	24.34	

3.1.2.2 Female Breast Cancer - *in situ*

Across the different clinical trial pools, Mantel-Haenszel-adjusted rate ratios for *in situ* female breast cancer (Table 4) ranged from 1.39 (95% CI, 0.15-13.40) when only positively adjudicated events in Pool 1b were analyzed to 2.09 (95% CI, 0.26-17.03) in Pools 1a, 1b, and 3 (MedDRA). No *in situ* breast cancers occurred in the diabetes trials (Pool 2) and none of the associations in other trial pools reached statistical significance.

Table 4. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for *in situ* Female Breast Cancer Cases Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	Events, n	4	1
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.08	
1b	Events, n	4	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.69	
2	Events, n	0	0
	Pt-years	3,028.3	856.8
	RR _{MH}	--	
	95% CI	--	
	RD _{MH}	0	
3	Events, n	4	1
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	4.13	
Adjudicated			
1b	Events, n	3	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	1.39	
	95% CI	0.15-13.40	
	RD _{MH}	2.42	

3.1.3 Colorectal Cancer

Across all clinical trials (Table 5, Pool 3), 10 colorectal cancers (MedDRA) occurred among patients exposed to liraglutide and 2 among patients in comparator arms, resulting in a statistically non-significant Mantel-Haenszel-adjusted rate ratio of 2.03 (95% CI, 0.42-9.71). In the weight management pool with trials that included adjudication (Pool 1b) 2 and 0 events (MedDRA) were counted in patients on liraglutide or comparator, respectively, but 2 and 1 events, respectively, were positively adjudicated. No increased risk was evident in the analysis of positively adjudicated events in Pool 1b (RR_{MH} , 0.82; 95% CI, 0.07-9.90), but the 95% confidence interval was wide.

Table 5. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Colorectal Cancer Cases Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA							
1a	Events, n	2	0	1	0	1	0
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1821.1
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.36		4.92		2.60	
1b	Events, n	2	0	1	0	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1669.2
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.68		5.34		2.86	
2	Events, n	8	2	5	1	3	1
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	1.62		1.91		1.05	
	95% CI	0.33-8.03		0.21-17.36		0.11-9.61	
	RD _{MH}	6.28		8.20		0.65	
3	Events, n	10	2	6	1	4	1
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	2.03		2.22		1.47	
	95% CI	0.42-9.71		0.25-19.83		0.18-12.24	
	RD _{MH}	4.67		7.01		1.97	
Adjudicated							
1b	Events, n	2	1	1	1	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	0.82		0.32		--	
	95% CI	0.07-9.90		0.01-7.62		--	
	RD _{MH}	-0.81		-11.40		2.86	

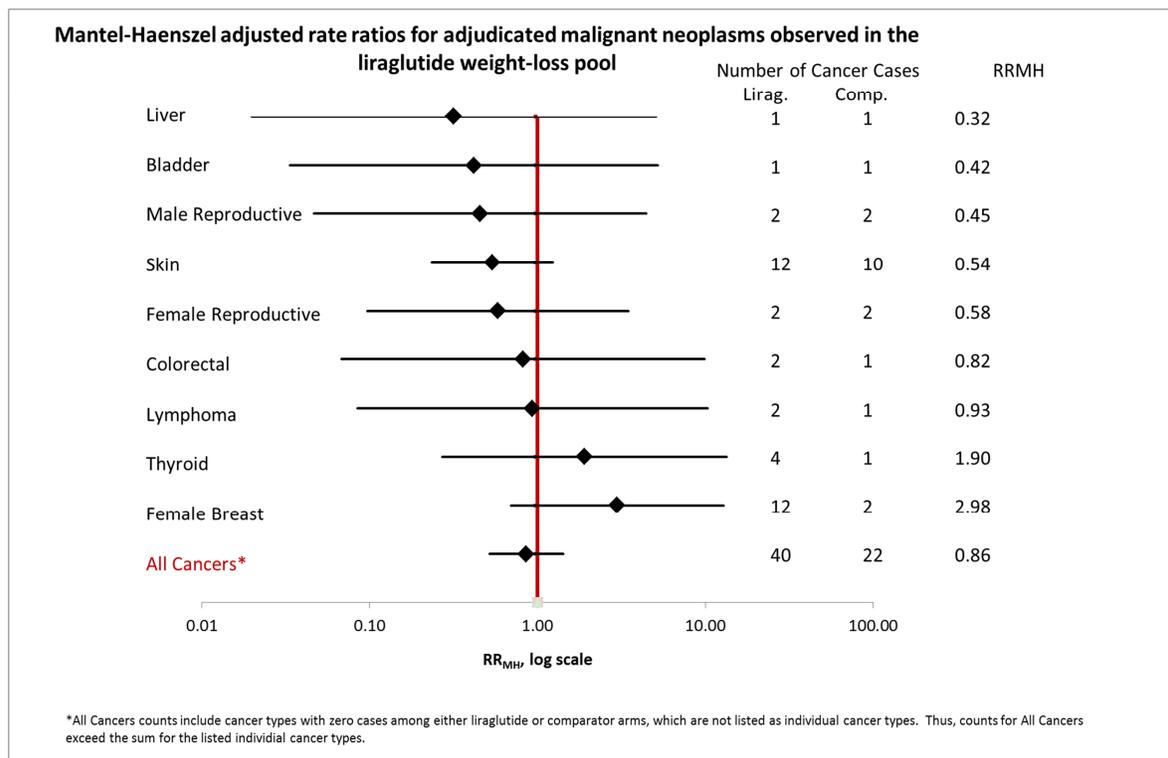
3.1.4 All Cancers

This section summarizes Mantel-Haenszel-adjusted rate ratios by cancer type for all cancers diagnosed in Pool 1b (adjudicated, Section 3.1.4.1) and in Pool 3 (MedDRA, Section 3.1.4.2).

3.1.4.1 Trial Pool 1b - Adjudicated Cases

Among all cancer types analyzed in Pool 1b (Figure 1), only thyroid cancer and female breast cancer (excluding *in situ*) occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms. Liraglutide was not associated with an increased risk for all adjudicated cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42), but the 95% confidence interval includes the possibility of a modest increase or decrease in cancer risk. Event counts were small for most cancer types, resulting in wide confidence intervals.

Figure 1. Mantel-Haenszel-Adjusted Rate Ratios for Adjudicated Malignant Neoplasms Observed in the Liraglutide Weight Management Pool

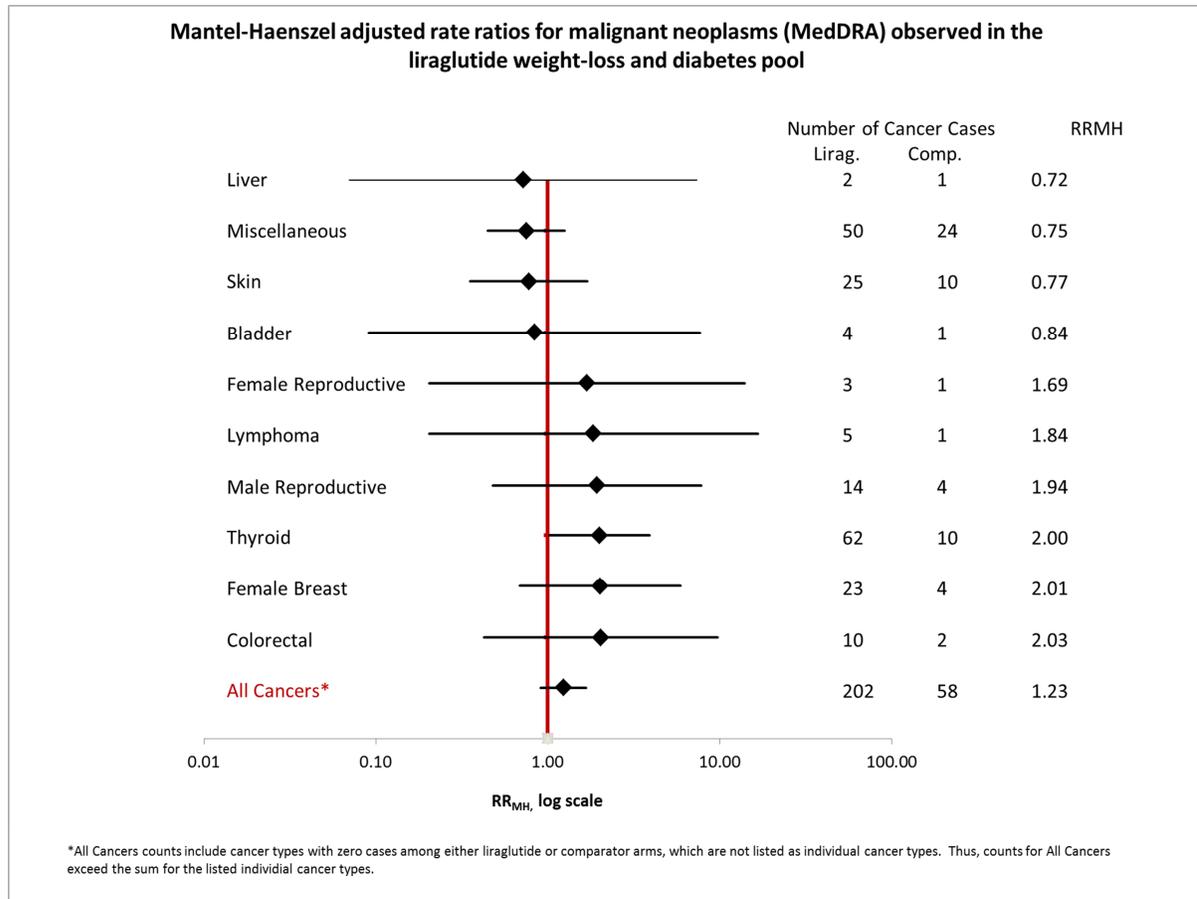


3.1.4.2 Trial Pool 3 – Cases based on MedDRA

Across the liraglutide trials in the weight management and diabetes pool (Pool 3, Figure 2), 202 cancer events occurred among patients exposed to liraglutide and 58 among patients exposed to comparators (RR_{MH} , 1.23; 95% CI, 0.91-1.67). These events were detected using MedDRA coding, without adjudication. Mantel-Haenszel-adjusted rate ratios were elevated for cancers of the male and female reproductive systems, lymphoma, thyroid cancer, female breast cancer (excluding *in situ*), and colorectal cancer. Neither

the cancer type-specific associations nor the association for all cancers reached statistical significance.

Figure 2. Mantel-Haenszel-Adjusted Rate Ratios for Malignant Neoplasms (MedDRA) Observed in the Liraglutide Weight Management and Diabetes Pool



3.2 EXTERNAL COMPARISONS

3.2.1 Thyroid Cancer

Across all study pools, regardless of sex, exposure status, or method of ascertainment (MedDRA or EAC adjudication), thyroid cancer was more common in the liraglutide clinical trials than what would be expected in the U.S. population with a comparable sex- and age distribution (Table 6). Standardized incidence ratios were highest for males exposed to liraglutide in the diabetes program (SIR, 51.00, 95% CI, 33.43-74.73) where 24 MedDRA cases occurred but only 0.47 cases were expected. Smaller counts of EAC-adjudicated thyroid cancer cases in the weight management pool 1b resulted in smaller, but sometimes still statistically significant, SIRs (e.g., liraglutide, both sexes: SIR, 3.43; 95% CI, 1.09-8.27). Standardized incidence ratios were consistently higher among patients exposed to liraglutide compared to patients in comparator arms.

Table 6. Number of Thyroid Cancer Cases Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA							
1a	n(obs.)	16	4	6	0	10	4
	n(exp.)	1.31	0.61	0.16	0.07	1.15	0.54
	SIR	12.24	6.55	38.69	--	8.68	7.36
	95% CI	7.24-19.45	2.08-15.80	15.68-80.46	--	4.41-15.47	2.34-17.75
1b	n(obs.)	15	4	5	0	10	4
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	12.85	7.14	35.43	--	9.75	8.04
	95% CI	7.47-20.73	2.27-17.21	12.98-78.54	--	4.95-17.38	2.55-19.39
2	n(obs.)	46	6	24	3	22	3
	n(exp.)	1.44	0.42	0.47	0.15	0.97	0.28
	SIR	31.91	14.17	51.00	20.29	22.65	10.89
	95% CI	23.63-42.19	5.74-29.47	33.43-74.73	5.16-55.20	14.56-33.74	2.77-29.64
3	n(obs.)	62	10	30	3	32	7
	n(exp.)	2.75	1.03	0.63	0.21	2.12	0.82
	SIR	22.55	9.67	47.94	13.96	15.07	8.54
	95% CI	17.44-28.72	4.91-17.24	32.94-67.58	3.55-37.99	10.48-21.02	3.74-16.90
Adjudicated							
1b	n(obs.)	4	1	1	0	3	1
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	3.43	1.78	7.09	--	2.92	2.01
	95% CI	1.09-8.27	0.09-8.80	0.35-34.95	--	0.74-7.96	0.10-9.91

3.2.2 Female Breast Cancer

3.2.2.1 Female Breast Cancer (excluding *in situ*)

Female breast cancers (excluding *in situ*) occurred somewhat more commonly than expected among women exposed to liraglutide and somewhat less commonly than expected among women in comparator arms. Adjudication of cancer events did not alter these associations. In the weight management pool (Pool 1b), 12 EAC-adjudicated events occurred among women exposed to liraglutide, where 6.23 events would be expected (SIR, 1.92; 95% CI, 1.04-3.27). Two events occurred in the comparator arms, where 3.02 events would be expected (SIR, 0.66; 95% CI, 0.11-2.19). Standardized incidence ratios were somewhat higher in the weight management pools (Pools 1a and 1b), compared with the diabetes pool (Pool 2).

Table 7. Number of Female Breast Cancer Cases (not including *in situ*) Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	n(obs.)	14	3
	n(exp.)	6.98	3.27
	SIR	2.01	0.92
	95% CI	1.14-3.29	0.23-2.50
1b	n(obs.)	13	3
	n(exp.)	6.23	3.02
	SIR	2.09	0.99
	95% CI	1.16-3.48	0.25-2.70
2	n(obs.)	9	1
	n(exp.)	8.14	2.39
	SIR	1.11	0.42
	95% CI	0.54-2.03	0.02-2.07
3	n(obs.)	23	4
	n(exp.)	15.12	5.66
	SIR	1.52	0.71
	95% CI	0.99-2.25	0.22-1.71
Adjudicated			
1b	n(obs.)	12	2
	n(exp.)	6.23	3.02
	SIR	1.92	0.66
	95% CI	1.04-3.27	0.11-2.19

3.2.2.2 Female Breast Cancer - *in situ*

In situ female breast cancers were not reported during the diabetes program (Pool 2), and were relatively uncommon overall. Regardless, SIRs matched the pattern observed for invasive female breast cancers (Section 3.2.2.1), with modestly higher event counts observed than expected in the weight management pools (Pools 1a and 1b) and somewhat higher SIRs in women exposed to liraglutide compared with women in comparator arms. None of the SIRs reached statistical significance.

Table 8. Number of *in situ* Female Breast Cancer Cases Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	n(obs.)	4	1
	n(exp.)	1.99	0.94
	SIR	2.01	1.06
	95% CI	0.64-4.84	0.05-5.25
1b	n(obs.)	4	1
	n(exp.)	1.78	0.87
	SIR	2.25	1.16
	95% CI	0.72-5.43	0.06-5.70
2	n(obs.)	0	0
	n(exp.)	2.25	0.65
	SIR	--	--
	95% CI	--	--
3	n(obs.)	4	1
	n(exp.)	4.24	1.59
	SIR	0.94	0.63
	95% CI	0.30-2.27	0.03-3.10
Adjudicated			
1b	n(obs.)	3	1
	n(exp.)	1.78	0.87
	SIR	1.69	1.16
	95% CI	0.43-4.59	0.06-5.70

3.2.3 Colorectal Cancer

Observed counts of colorectal cancer were close to what would be expected in most study pools (Table 9). This was especially notable among EAC-adjudicated events in the weight management pool (Pool 1b), where SIRs among both patients exposed to liraglutide and patients in comparator arms were very close to 1.0. Compared with adjudicated endpoints, event counts according to MedDRA and resulting SIRs were only slightly higher and none of the SIRs reached statistical significance.

Table 9. Number of Colorectal Cancer Cases Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA							
1a	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.48	1.10	0.91	0.40	1.50	0.70
	SIR	0.81	--	1.02	--	0.67	--
	95% CI	0.14-2.67	--	0.05-5.04		0.03-3.30	--
1b	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	--	1.10	--	0.74	--
	95% CI	0.15-2.93	--	0.06-5.44		0.04-3.66	--
2	n(obs.)	8	2	5	1	3	1
	n(exp.)	5.65	1.74	3.64	1.14	2.01	0.60
	SIR	1.42	1.15	1.38	0.88	1.49	1.65
	95% CI	0.66-2.69	0.19-3.80	0.50-3.05	0.04-4.34	0.38-4.06	0.08-8.16
3	n(obs.)	10	2	6	1	4	1
	n(exp.)	8.12	2.84	4.61	1.53	3.51	1.31
	SIR	1.23	0.70	1.30	0.65	1.14	0.77
	95% CI	0.63-2.19	0.12-2.33	0.53-2.70	0.03-3.22	0.36-2.75	0.04-3.77
Adjudicated							
1b	n(obs.)	2	1	1	1	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	0.97	1.10	2.65	0.74	--
	95% CI	0.15-2.93	0.05-4.79	0.06-5.44	0.13-13.08	0.04-3.66	--

3.3 ADJUDICATION

Only Pool 1b contained both events detected using MedDRA and events adjudicated by the EAC, which allows for a comparison of these methods. This pool included a total of 62 events confirmed by the EAC as malignant neoplasms and 4 as premalignant breast neoplasms. The sponsor found 12 EAC confirmed malignant neoplasms that were not identified by the SMQ search “Malignant and unspecified tumors.” In contrast, 54 events identified by the SMQ search were reviewed but not confirmed by the EAC as malignant neoplasms. The sponsor listed the following reasons for events not being confirmed as malignancies:

- 34 events were “downgraded” by the EAC; these events were typically reported with unspecific terms such as “neoplasm” or “tumor.”
- 10 events were confirmed either as a pre-malignant (n=7, not including the 4 premalignant breast neoplasms), benign (n=2) or unclassified neoplasm (n=1).
- 2 events were confirmed as a malignant neoplasm, but due to discrepancies between the investigator-reported onset date and that assigned by the EAC, they only appear on the SMQ-based list (as having onset during treatment), and not on the list of EAC-confirmed malignant neoplasms (as the EAC assigned event onset prior to treatment initiation).
- 6 events captured by the SMQ search were confirmed as malignant neoplasms through linking to another EAC-confirmed malignant neoplasm (index event), but only the index event appears on the list of EAC-confirmed malignant neoplasms.
- 1 event was never sent for adjudication and 1 could not be adjudicated due to incomplete source documentation.

Dr. Jonathan Jarow, Medical Officer in the Division of Oncology Drug Products-I, reviewed the sponsor’s external adjudication procedures and found them acceptable.⁶ In fact, they were similar to the methods utilized in the collection of data for the SEER database.

4 DISCUSSION

Analyses presented in this review include internal and external comparisons of malignancies observed in various trial pools in the clinical development program of liraglutide.

Dr. Jonathan Jarow stated that the best safety population to utilize for describing the risk of cancer in the weight management program includes the adjudicated events from the four weight management trials (Pool 1b in this review).⁶ He further stated that using the larger data set, which also includes the diabetes trials (Pool 3 in this review), has the advantage of increased power, however, at the expense of reliability of event categorization. I agree with his statements. In addition, diabetes trials were of shorter duration (generally 26 weeks) than weight-loss trials (mostly 56 weeks or longer, Appendix Table 1), which makes the detection of a cancer-initiating or -promoting drug

⁶ Jonathan P Jarow. OHOP consult on liraglutide. June 24, 2014, available in DARRTS.

effect less likely. It is unfortunate that none of the events in the diabetes program were adjudicated. As a consequence, the pool with adjudication of malignancies (Pool 1b) included only 4 out of 30 clinical trials in the liraglutide development program, however, with approximately 39.2% of total person-time exposed to liraglutide and 50.8% of total person-time in comparator arms.

As presented in Section 3.1.4.1 and shown in Figure 1, using adjudicated events in Pool 1b, only thyroid cancer and female breast cancer occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms, albeit not statistically significantly. However, liraglutide was not associated with an increased risk of all cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42). In addition, point estimates for individual cancer types ranged from decreased rates for some to increased rates for other cancers. This is not unexpected in a multiple hypothesis testing situation, even in the absence of a treatment effect on the outcome of interest. Nevertheless, although these findings are somewhat reassuring, this analysis cannot exclude the possibility of a causal effect of liraglutide on thyroid cancer or female breast cancer.

With regard to colorectal cancer, staff of DMEP observed an imbalance in benign events. However, the scope of this review was limited to malignant events, which were balanced between patients exposed to liraglutide and comparators.

External comparisons showed substantially more new diagnoses of thyroid cancer (MedDRA) than would be expected based on age- and sex-standardized U.S. population rates. However, for thyroid cancer, adjudication rates were low. Of 15 and 4 cases (MedDRA) observed in Pool 1b among patients exposed to liraglutide and comparators, respectively, only 4 and 1 cases, respectively, were positively adjudicated. The SIR of adjudicated thyroid cancer events, regardless of exposure status, was much smaller, but in the case of liraglutide-exposed patients still statistically significant. SIRs for female breast and colorectal cancer showed only modest deviations between observed and expected counts. Given the limitations inherent in external comparisons as listed below, modest deviations between observed and expected counts should be interpreted with caution.

Several considerations should be kept in mind when interpreting the data presented in this review. First, these analyses included all cancer cases diagnosed during follow-up, without consideration of induction times. For cancer cases that were diagnosed shortly after study initiation, a cancer-inducing or even -promoting effect of study treatment may be questionable. I refer to Dr. Jarow's review, which includes additional detail and discussion of the timing of malignant events.⁶ Second, in the calculation of person-time, individual follow-up was not censored at the time of a cancer diagnosis. Ordinarily, the time after diagnosis should not be considered time at risk and, therefore, not be included in the denominators of incidence rate calculations. However, for simplicity and to use consistent denominators in the analyses of different cancer types, all available person-time was used. Because of the relative rarity of the endpoints of interest, including or not including person-time after diagnosis will have little effect on the total person-time and the calculation of incidence rates.

In addition to the aforementioned considerations, comparisons between treatment arms of clinical trials and an external standard (i.e. U.S. SEER data) are subject to inherent

limitations. Several factors can bias these comparisons either towards higher or lower rates in clinical trials compared with the external standard and some factors could impact clinical trial rates in either direction.

The following factors could potentially lead to higher cancer rates in the reviewed clinical trials compared with U.S. SEER data:

- Association of diabetes and obesity with increased risk of certain cancer types,⁷ including thyroid cancer,^{8,9} breast cancer,¹⁰ and colorectal cancer^{11,12}
- Surveillance bias due to regularly scheduled follow-up visits
- Detection bias related to labeling of liraglutide for thyroid cancer
- Detection bias due to drug effects (e.g. weight loss can facilitate detection of breast cancer; in fact, SIRs for breast cancer were higher in weight-loss than in diabetes pools)
- Inclusion of non-adjudicated events (MedDRA)
- Inclusion of both malignant and unspecified events in analyses based on MedDRA search terms, while U.S. SEER data only included malignant neoplasms
- Inclusion of MedDRA events that were not limited to index events (i.e. primary cancer)
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

The following factors could potentially lead to lower cancer rates in the reviewed clinical trials compared with U.S. SEER data:

- Voluntary participation can result in the selection of healthier patients with higher socioeconomic status and better access to healthcare and prevention
- Inclusion and exclusion criteria may result in a sample at lower risk for cancer
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

Although these factors can bias the results in opposing directions, their relative magnitude is difficult to predict and it would be imprudent to assume that they cancel

⁷ Renehan AG et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–78.

⁸ Kitahara CM et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of 5 prospective studies. *Cancer Epidemiol Biomarkers Prev.* 2011 March; 20(3): 464–472.

⁹ Meinhold CL et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* 2010; 171:242–252.

¹⁰ DeSantis C et al. Breast cancer statistics, 2013. *CA Cancer J Clin.* 2014 Jan-Feb; 64(1):52-62.

¹¹ Jiang Y et al. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol.* 2011; 26:863–876.

¹² Larsson SC et al. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005; 97 (22): 1679-1687.

each other out. As a consequence, SIRs resulting from comparisons with an external standard are subject to systematic error and should be interpreted with caution.

5 CONCLUSION

Internal comparisons based on clinical trial data suggest the possibility of increased rates of thyroid cancer and female breast cancer among patients exposed to liraglutide compared with patients in comparison arms. However, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers. However, comparisons between clinical trial data and a reference population should be carefully interpreted.

6 RECOMMENDATIONS

A post-marketing observational study is currently ongoing to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to liraglutide (PMR 1583-6), of which DEPI-I has recently reviewed an interim report and posed questions to the sponsor.¹³ Conduct of a separate study focused on a weight-loss indication may be challenging due to limited ability to detect the indication in electronic healthcare data, despite different doses of the drug and different product names used for diabetes and proposed for weight loss. Should liraglutide be approved for weight loss, I do not recommend a separate observational study for cancer with the use of liraglutide as a weight-loss agent.

A cardiovascular outcomes trial is currently underway for liraglutide in the treatment of diabetes (PMR 1583-9). In it, the FDA required the sponsor to also assess long-term effects of Victoza, including neoplasms. If a separate cardiovascular outcomes trial is being considered for liraglutide as a weight-loss agent, it should include adjudication and analysis of malignant neoplasms.

I recommend that DMEP consider adding the observed imbalances in thyroid and female breast cancer in humans to the labeling of Victoza and Saxenda, together with a description of the uncertainty surrounding these estimates.

Christian Hampp, PhD

¹³ Christian Hampp. Year-3 interim report of observational safety study of liraglutide, PMR 1583-6. June 27, 2014, available in DARRTS.

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APPENDIX

Table 1. Clinical Trials in the Liraglutide Weight Management Program (Table 1-1, Saxenda 120-day Safety Report, April 15, 2014)*

Trial ID Phase	Duration of treatment	Population	Doses (mg) ^a	N ^b (SAS)	Trial design features including follow-up period/ Randomization
<i>Completed trials</i>					
<i>Clinical pharmacology</i>					
3630 Phase 1	5 weeks	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0 or 1.8 mg, Placebo	49 (total)	2-week follow-up/ Two-period balanced 6 sequence incomplete cross-over design with minimum 7 subjects in each treatment sequence
<i>Phase 2 and 3</i>					
1807 Phase 2	20 weeks + 84-week extension	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0, 2.4, 1.8, or 1.2 mg Orlistat 120 mg TID Placebo	564 (total), 98 to placebo, 95 to orlistat, 371 to liraglutide	Weeks 20–52 (single-blind): Subjects continued on their randomized treatment. Weeks 52–104 (open-label): Liraglutide/placebo-treated subjects switched to liraglutide 2.4 mg and then 3.0 mg as sites received Ethics Committee approval. Orlistat-treated subjects continued on orlistat. 2-week follow-up period after trial completion. Randomization: 1:1:1:1:1
1839 Phase 3 56-week (main part of trial)	56 weeks	BMI: ≥30 kg/m ² or ≥27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg, Placebo	3723 (total), 1242 placebo, 2481 liraglutide	Subjects without pre-diabetes at screening: After completion of 56-week treatment period, liraglutide-treated subjects were re-randomized to either continue liraglutide or switched to placebo in the following 12 weeks Placebo-treated subjects continue on placebo. Randomization: 2:1
1922 Phase 3	56 weeks	BMI: ≥27 kg/m ² with T2DM	Liraglutide 3.0, 1.8 mg Placebo	844 (total), 212 placebo, 210 liraglutide 1.8 mg, 422 liraglutide 3.0 mg	12-week observational follow-up period after trial completion. Randomization: 2:1:1

*Trials included in analyses of malignant neoplasms are highlighted in yellow.

Table 1 continued

Trial ID Phase	Duration of treatment	Population	Doses (mg) ^a	N ^b (SAS)	Trial design features including follow-up period/ Randomization
3970 Phase 3	32 weeks	BMI: ≥ 30.0 kg/m ² with moderate or severe OSA. T2DM excluded	Liraglutide 3.0 mg Placebo	355 (total), 179 placebo, 176 liraglutide 3.0 mg	2-week follow-up period after trial completion. Randomization: 1:1
1923 Phase 3	56 weeks	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia and/or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	422 (total) 210 placebo 212 liraglutide 3.0 mg	Maintenance of weight loss (min. 5%) achieved during a 4-12 week run-in using a low-calorie diet. 12-week observational follow-up period after trial completion. Randomization: 1:1
Ongoing trials					
3967 Phase 1 Ongoing	5-6 weeks	BMI: Corresponding to ≥ 30 kg/m ² for adults ^c Age: 12-17 years with Tanner stage 2-5 pubertal development	Liraglutide 3.0 mg Placebo	21 (total)	2-week follow-up Randomization: 2:1
1839-ext Phase 3 (104-week extension ongoing)	3 year: 56 weeks + 104- week	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	1584 (total) 497 placebo 1087 liraglutide 3.0 mg	Subjects with pre-diabetes at screening: Treated for up to 3 years (including the 104-week extension period), followed by a 12-week observational follow-up period.

BMI: body mass index; OSA: obstructive sleep apnea; T2DM: type 2 diabetes mellitus; TID: *ter in die*.

a. Once-daily dose with dose-escalation of liraglutide in weekly steps of 0.6 mg in all weight management trials (starting dose: 0.6 mg). **b.** Number of treated subjects. **c.** BMI corresponding to ≥ 30 kg/m² for adults by international cut-off points² and ≤ 45 kg/m² and $\geq 95^{\text{th}}$ percentile for age and sex

Table 2. Clinical Trials included in the Analyses of Malignant Neoplasms

Trial ID	Liraglutide		Comparator		Trial Pool			
	pts. (n)	p-yrs.	pts. (n)	p-yrs.	1a	1b	2	3
NN1250-3948	87	42.3	0*	0*			X	X
NN2211-1310	135	32.3	55	13.0			X	X
NN2211-1332	13	1.9	13	2.1			X	X
NN2211-1333	21	3.7	12	2.1			X	X
NN2211-1334	180	57.5	46	13			X	X
NN2211-1436	695	337.6	345	159.1			X	X
NN2211-1499	72	8.0	72	8.1			X	X
NN2211-1571	123	33.7	40	9.3			X	X
NN2211-1572	724	1022	363	446.5			X	X
NN2211-1573	497	782.2	248	330.3			X	X
NN2211-1574	355	157.2	175	73.4			X	X
NN2211-1697	230	112.3	346	172.3			X	X
NN2211-1700	268	249.4	132	123.6			X	X
NN2211-1701	176	172.6	88	76.3			X	X
NN2211-1796	697	201.6	231	74.1			X	X
NN2211-1797	421	448.4	232	103.5			X	X
NN2211-1799	16	4.2	33	8.6			X	X
NN2211-1842	987	971.4	0	0			X	X
NN2211-1860	573	550.6	219	182.4			X	X
NN2211-2072	176	41.4	34	8.5			X	X
NN2211-3924	240	233	120	117.8			X	X
NN2211-3925	127	88.3	130	89.8			X	X
NN8022-1807	433	559.4	193	197.4	X			X
NN8022-1839	2,481	3,714.3	1,242	1,730.1	X	X		X
NN8022-1922	632	721.3	212	229	X	X		X
NN8022-1923	212	233.4	210	223.4	X	X		X
NN8022-3970	176	97.2	179	104.4	X	X		X
NN9068-3697	1,237	1071	0*	0*			X	X
NA NN9068-3912	199	96.8	0*	0*			X	X
NN9535-1821	95	27.8	46	14.6			X	X
Total	12,278	12,072.8	5,016	4,512.7				

*comparator groups with insulin degludec or semaglutide not included

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/s/

CHRISTIAN HAMPP
07/25/2014

DIANE K WYSOWSKI
07/25/2014

DAVID C SHIH
07/25/2014

HUMAN FACTORS, LABEL, AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 22, 2014
Requesting Office or Division: Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number: NDA 206321
Product Name and Strength: Saxenda (Liraglutide) Injection, 6 mg/mL
Product Type: Combination (Drug + Device)
Rx or OTC: Rx
Applicant/Sponsor Name: Novo Nordisk
Submission Date: December 20, 2013
OSE RCM #: 2014-78
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested DMEPA evaluate the Applicant's Human Factor Validation Study Results as well as the container label, carton labeling, and Instructions for Use (IFU) associated with the proposed product Saxenda (liraglutide), to ensure the intended population is able to use the product safely and effectively.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	B
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors Study: Usability

In terms of usability, human factors study results demonstrated that Saxenda prefilled pen can be used safely and effectively by trained users. However, some untrained users encountered difficulties while administering this product using the prefilled pen. The difficulties the untrained user group encountered have also been reported with the use of other prefilled injection pen devices and have been managed reasonably well through labeling. Additionally, the types of observed errors are not unique to the proposed pen (i.e. did not check flow before first injection, dose not set correctly, checks flow with dose and does not reset dose, etc.). Failure to perform these tasks would result in underdoses in most instances and would not be expected to cause serious harm acutely. The PDS290 pen-injector platform that is proposed for this product has been approved for Novolog and Levemir.

Human Factors Study: Differentiation

During the differentiation part of the HF study, there were two failures where the participants chose the Victoza carton or pen. A pharmacist, who did not see the (b) (4) (Brand name used for Saxenda during the human factors study) carton, chose the Victoza carton after checking that the established name was correct. An untrained elderly patient who indicated that he was not sufficiently observant and did not expect the refrigerator to contain other types of pen-injectors, chose the Victoza pen relying on colors and his memory. Thus, both failures are artifacts of the study.

Overall, we find the results of the human factors study acceptable. However, we recommend that training be provided before first use of the product to ensure safe and effective use of the device to deliver the dose of liraglutide for the proposed indication due to the errors that have occurred with some untrained users and since weight management is not typically managed with injectable drugs.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Study demonstrated that trained users are able to use the prefilled pen safely and effectively. However, some untrained users may encounter difficulties while administering this product. As a result, DMEPA concludes that proper education and training prior to first injection of liraglutide for the proposed indication is desirable to promote the correct use of the product.

The proposed IFU, container label, carton and insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR NOVO NORDISK

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Physician Insert: Section 2 Dosage and Administration
 - 1. Add the statement: “Prior to initiation of SAXENDA, patients should be trained by their healthcare professional on proper injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.”
- B. Carton Labeling, Pen Label, Package Insert Labeling, and IFU
 - 1. Remove all trailing zeros throughout the label and labeling. The trailing zero after the decimal point may lead to misinterpretation (e.g. 3.0 mg as 30 mg). Trailing zeros are listed as a dangerous dose designation on the Institute of Medicine’s ‘List of Error-Prone

Abbreviations, Symbols, and Dose Designations'¹. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.

¹ <https://www.ismp.org/tools/errorproneabbreviations.pdf> (last accessed 4/22/14)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Saxenda that Novo Nordisk submitted on December 20, 2013.

Table 2. Relevant Product Information for Saxenda			
Active Ingredient	Liraglutide		
Indication	As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of <ul style="list-style-type: none"> •30 kg/m² or greater (obese) or •27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea 		
Route of Administration	Subcutaneous injection		
Dosage Form	Solution		
Strength	6 mg/mL		
Dose and Frequency	The maintenance dose is 3 mg once daily. Dose escalation to reach the maintenance dose of 3 mg is 0.6 mg, 1.2 mg, 1.8 mg, and 2.4 mg (the patient should stay on each dose for 7 days)		
How Supplied	3 or 5 prefilled pen		
Storage	Prior to first use		After first use
	Refrigerated 36°F to 46°F (2°C to 8°C)		Room Temperature 59°F to 86°F (15°C to 30°C)
	Until expiration date		Refrigerated 36°F to 46°F (2°C to 8°C)
		30 days	
Container Closure	PDS290 pen-injector for liraglutide is a pen-shaped, prefilled device containing a 3 ml cartridge with the drug liraglutide. Therefore, the drug is not in contact with the device. The device is intended to function with a standard needle thread or a needle with a bayonet coupling.		

APPENDIX B. HUMAN FACTORS STUDY

B.1 Study Design

Study Participants

Training consisted of receiving 30-45 minutes of one-on-one, hands-on training and watching a training video with a 17-minute runtime. The duration and nature of the training provided test participants with the representative training that Novo Nordisk expects end-users to receive upon product launch. A nurse educator experienced in injection training trained the participants. The participants then returned 1-36 hours later to participate in a test session lasting up to one hour and 15 minutes.

Table 4: Summary of participant demographic characteristics

	Total number of participants	Age (range and mean)	Sex		Training		Injection experience	
			Male	Female	Trained	Untrained	Experienced	Naive
Adult	64	26 to 64 Mean: 46.2	25	39	33	31	33	31
Elderly	65	65 to 84 Mean: 68.9	35	30	34	31	35	30
Healthcare Professionals	34	25 to 66 Mean: 47.5	11	23	0	34	N/A	N/A
Total	163		71	92	67	96	68	61

Protocol

Task 1a (carton retrieval - patient participants):

- Take your new medication box out of the refrigerator, bring it back to the table and confirm that you have chosen the right product.

Task 1b (carton retrieval – non-pharmacist HCPs):

- Retrieve the (b) (4) carton box from the refrigerator, confirm that you have chosen the right product.

Task 1c (carton retrieval – pharmacists):

- Retrieve (b) (4) liraglutide for injection 6 mg/mL, confirm that you have chosen the right product.

Task 2a (pen-injector retrieval – patient participants):

- Select your pen-injector from the container. Remove the pen-injector cap, confirm that you have chosen the right product.

Task 2b (pen-injector retrieval – non-pharmacist HCPs):

- Retrieve the (b) (4) pen-injector from the container. Remove the pen-injector cap, confirm that you have chosen the right product.

Task 3 (Check clarity of drug):

- Check that the medication in your (b) (4) pen-injector is clear and colorless. Describe how you made this determination.

Task 4 (normal injection):

- Deliver 1.2 mg of the medication using the (b)(4) pen-injector.

Task 5 (Dose reversal):

- Deliver 3.0 mg of the medication using the (b)(4) pen-injector. [To mimic dose reversal the test administrator asked participants to:] Deliver 1.8 mg instead.

Task 6 (end-of-content): The test administrator provided a pen-injector containing slightly more than 1.2 mg, and instructed participants to imagine that they had been using the pen-injector for some time now.

- Deliver 2.4 mg of the medication using the (b)(4) pen-injector.

Condition	Step to test	Test priority	Severity class*
Scenario 1 – User does not receive the correct drug due to mix-up (all user groups will be tested)			
Steps are performed at dispensing, e.g. at the pharmacy, and at home: Normal test conditions Untidy or illogical storage system (only for pharmacies)	Step 1: Pick the PDS290 liraglutide 3.0 mg carton/pen-injector.	1	S4 – S5
	Step 2: Pen cap removal (Not pharmacists.)	3 (Not safety-related)	S1 – S2
	Step 3: Verify via label and cartridge holder it is the correct pen (Not pharmacists)	1	S4 – S5
Scenario 2 – The user does not administer the injection as intended (all user groups will be tested except pharmacists)			
All steps performed at home: Normal test conditions Naturally present dexterity and visual impairments.	Step 2: Pen cap removal	3 (Not safety-related)	S1 – S2
	Step 3: Verify via label and cartridge holder that it is the correct pen	1	S4 – S5
	Step 4: Check that the drug is clear and colourless	2	S3
	Step 5: Needle mounting	2	S3
	Step 6: Checking the drug flow (this step only applies before the first injection with each new pen)	3 (Not safety-related)	S1 – S2
	Step 7: Setting the intended dose (reversing the dose setting, if necessary)	2	S3
	Step 8: Understand the EOC indication (feature ensuring that no larger dose can be dialled than is left in the cartridge. This step only applies if the user is going to inject a dose larger than the remaining left in cartridge.)	2	S3
	Step 9: Subcutaneous needle insert	3 (Not safety-related)	S1 – S2
	Step 10: Injecting the dose, including leaving the needle in the skin after the dose counter has returned to 0 and counting slowly to 6	2	S3
	Step 11: Needle removal and disposal of used needle	2	S3
	Step 12: Pen cap mounting	3 (Not safety-related)	S1 – S2

*The severity class is based on the worst case scenario of each step

B.2 Results

Needle stick injury

Table 6-2 Overview of task failure occurrences for trained participants

Task failure description	No. of task failures	Clinical evaluation of task failures
Needle stick injury	1	Minor pain

Table 6-3 Overview of task failure occurrences for untrained participants

Task failure description	No. of task failures	Clinical evaluation of task failures
Needle stick injury	5	Minor pain

Table 6-4 Overview of use errors related to handling with no potential for harm or impact on the prescribed therapy - Trained participants

Use error description	No. of use errors	Clinical evaluation of use errors
Did not flow check before first injection	11	In the worst case, a single underdose with no or insignificant medical consequences
Flow checks with dose and does not reset the dose	1	

Table 6-5 Overview of use errors related to handling with no potential for harm or impact on the prescribed therapy - Untrained participants

Use error description	No. of use errors	Clinical evaluation of use errors
Did not remove inner and/or outer needle cap(s) before injecting	19	In real life, not relevant since patients would realise that the needle did not pierce their skin due to the lack of tactile sensation from the needle entering their skin
Did not flow check before first injection	29	In the worst case, a single underdose with no or insignificant medical consequences
Dose not set correctly	8	
Flow checks with dose and does not reset the dose	7	
Did not remove needle after use	5	
Dose not set	4	
Needle is not fully inserted prior to injection start	3	
Dose button not held down until dose counter returns to "0"	2	
Picked Victoza [®] liraglutide carton	1	
Picked Victoza [®] liraglutide pen-injector	1	

Differentiation

One of 163 participants retrieved the Victoza[®] carton from the refrigerator, rather than the (b) (4)[®] carton (1 untrained pharmacist). The pharmacist was not sure if he retrieved the correct medication (task instruction had (b) (4) but he retrieved Victoza) but upon conferring the active ingredient and the concentration on the task card, he confirmed that Victoza was the correct medication. The pharmacist stated that he did not check the other cartons in the refrigerator assuming that each stack of cartons (3 stacks) was for the same medication (as is in his pharmacy). In the real world, the pharmacist would be aware of the products that are available in the pharmacy and how they are organized.

One of 145 participants retrieved the Victoza[®] pen-injector from the container, rather than the (b) (4)[®] pen-injector (1 untrained injection-experienced elderly). The participant selected the Victoza pen, removed the cap, recognized he selected the wrong pen, selected (b) (4) pen next, removed the cap and determined it was not his new medication. He then selected the Apidra pen, compared to Victoza pen and incorrectly confirmed Victoza pen was his medication. He relied on his memory of the colors of the vial, cartridge housing, and the dose button instead of comparing the names. The participant also reportedly was not sufficiently observant and did not expect the refrigerator to contain other types of pen-injectors. This is an

artifact of the study since the patient did not remember the name of the medication but was focusing on the appearance of the pen.



Figure 17. The Victoza[®] (top) and (b) (4) pen-injector's light blue colours are similar in appearance.

Table 6-6 Overview of close call occurrences for trained and untrained participants

Close call observed (i.e. description of the use error that almost occurred)	Number of Close calls	
	Trained	Untrained
Initially picked Levemir® FlexTouch® basal insulin	2	3
Almost did not set dose correctly	2	2
Initially did not flow check before first injection	1	2
Almost did not remove inner needle cap prior to injecting	1	2
Almost did not hold dose button down until dose counter is back to "0"	1	2
Initially did not remove needle after use	1	0



Figure 19. The (b) (4) pen-injector (top) is a light blue colour, and the Levemir® pen-injector (bottom) is dark blue.

Table 6-7 Overview of operational difficulty occurrences for trained and untrained participants

Operational difficulties (i.e. description of the experienced difficulty that occurred)	Number of Operational difficulties	
	Trained	Untrained
Attaching needle to pen-injector	1	6
Removing needle after an injection	1	6
Checking pen-injector flow	2	3
Removing outer needle cap	0	1
Removing inner needle cap	0	1

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Saxenda labels and labeling submitted by Novo Nordisk on December 20, 2013.

- Container label
- Carton labeling
- Instructions for Use
- Medication Guide

C.2 Label and Labeling Images

Sample



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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SARAH K VEE
07/22/2014

YELENA L MASLOV
07/22/2014

MEMO OF SPONSOR RESPONSES REVIEW

NDA 206321

FROM:	Sajjad H Syed, Electrical Engineer (CDRH General Hospital Devices Branch), 301-796-6295, sajjad.syed@fda.hhs.gov
TO:	Ms. Patricia Madara - OMPT/CDER/OND/ODEII/DMEP
DATE:	Wednesday April 16 th , 2014
SUBJECT:	Device Responses Review (ICC1400007/S004) PDS290 Liraglutide 3.0 mg pen-injector (NDA 206321)

CDRH/ODE Sponsor Responses Review:

The sponsor has responded back to the Agency letter which was sent to the sponsor on March 4th, 2014. The questions in the letter, sponsor responses (March 20th, 2014) and their assessments are shown below:

1. The Center for Devices and Radiological Health (CDRH) is unclear if subject device (PDS290 Liraglutide 3.0 mg pen-injector) is intended for delivery of a single cartridge, or is intended for long-term, multi-cartridge use. Please clarify this point for us.

Sponsor Response (March 4th, 2014): *Novo Nordisk would like to clarify that the PDS290 liraglutide 3.0 mg pen-injector is a pre-filled, disposable pen-injector which contains a 3 ml cartridge with liraglutide (6 mg/mL) for single patient use. The PDS290 liraglutide 3.0 mg pen-injector can deliver multiple doses - 0.6 mg, 1.2 mg, 1.8 mg, and 2.4 mg (titration doses) or 3.0 mg (maintenance dose). (Ref. M3, 3.2.P.7) The PDS290 liraglutide 3.0 mg pen-injector is not intended for long term multi-cartridge use.*

Consultant Assessment: *The sponsor has clarified now that the subject device (pen-injector) is only for single patient use and is not refillable, cartridge replaceable. --- Acceptable.*

2. You marked Biocompatibility as N/A for the subject device (PDS290 Liraglutide 3.0 mg pen-injector) stating that "Only external skin contact during injection". For the pen injector component of the drug, Liraglutide, please indicate if the cartridge or the needle that will contact the drug is changed due to the new dose proposed.

Sponsor Response (March 4th, 2014): *Novo Nordisk would like to clarify that neither the cartridge nor the needle that is in contact with the drug product is changed due to the new dose proposed. Moreover, both the cartridge and the*

needle are currently approved by the FDA for use with Victoza® (liraglutide [rDNA origin] injection), NDA 022341.

Consultant Assessment: The sponsor has clarified that both the cartridge and the needle are exactly the same as the currently approved cartridge/needle used in Victoza NDA 022341. --- **Acceptable.**

3. [REDACTED] (b) (4).
Please provide a list of all the materials used in the manufacture of all the components of the subject pen injector. The list should include [REDACTED] (b) (4), etc., used in the manufacturing of the subject device. In addition, please provide their Material Safety Data Sheets for evaluation.

Sponsor Response (March 4th, 2014): The complete list of component materials that have been used for the manufacturing of the subject device PDS290 liraglutide 3.0 mg pen-injector and their Material Safety Data Sheets are provided in Appendix D (of the responses).

Components	Base Materials	Additives
[REDACTED] (b) (4)		

Components	Base Materials	Additives
(b) (4)		

The PDS290 pen-injector consists of the (b) (4) items described in Table 1. Furthermore, the PDS290 liraglutide 3.0 mg pen-injector also utilizes a 3 ml cartridge (b) (4) and an injection needle ((b) (4)) shown in Figure 1.

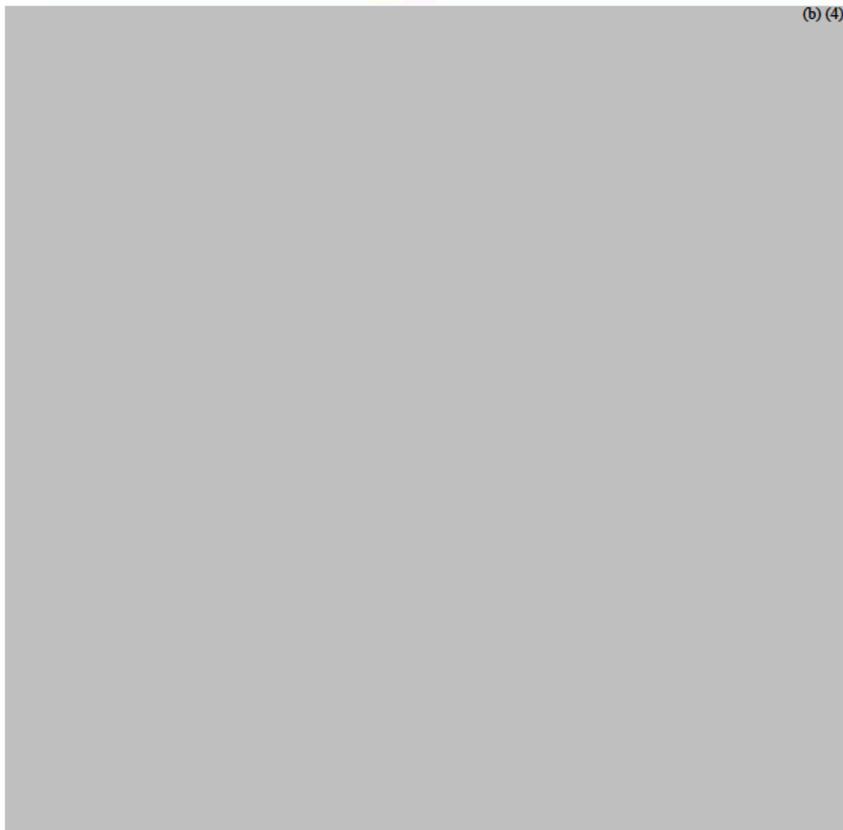


Figure 1: Exploded view of the PDS290 liraglutide 3.0 mg pen-injector (not shown in true colors).

Consultant Assessment: Dr. Rakhi Dalal (Microbiologist ODE/DAGRID/GHDB) reviewed the sponsor information above. In her email (dated April 14th, 2014) she stated that “Novo Nordisk in response to Deficiency 8-10 informed that neither the cartridge nor the needle that is in contact with the drug product has changed, and that the materials remained intact for the new proposed dose. Also, both the cartridge and the needle are currently approved by the FDA for use with Victoza® (liraglutide [rDNA origin] injection), NDA 022341. MSDS for the materials used is also provided, response to Deficiency 10. I agree with your analysis in regards to sponsor’s response to March 4, 2014 FDA letter, Deficiencies 8-10. Additional testing as previously requested may not be necessary”. --- **Acceptable.**

Dose Accuracy Review:

Please also note that Dr. Patricia Beaston (Endocrinologist CDRH/ODE/DAGRID/GHDB) reviewed the device dose accuracy as well. The sponsor stated (PDS290 pen-injector for liraglutide 3.0 mg - Summary Report of Qualification Testing - container-closure-system-summary.pdf) that “the dose accuracy was investigated at three dose sizes; dose 0.6 mg, 1.8 mg and 3.0 mg representing the minimum, midpoint and maximum dose, respectively”.

Reviewing the Agency recognized standard (ISO 11608-1: Needle-based injection systems for medical use — Requirements and test methods - Part 1: Needle-based injection systems), the sponsor has tested the pen-injector at each of the three pre-set doses.

The accuracy is defined as $U = V_{set} + (\beta \cdot V_{set})/100$; $L = V_{set} - (\beta \cdot V_{set})/100$.

The sponsor conducted the testing based on the accuracy limits and provided the results in the table. Given the results, the PDS290 pen-injector for liraglutide 3.0 mg **complies** with the dose accuracy tolerance limits according to ISO 11608-1:2012.

In light of the additional information provided by the sponsor on March 20th, 2014, CDRH/ODE/DAGRID/GHDB does not have any additional device biocompatibility, safety, performance questions.

Sajjad H. Syed
-S

Digitally signed by Sajjad H. Syed -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Sajjad H. Syed -S,
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Date: 2014.04.16 14:10:04 -04'00'

Sajjad H. Syed
Electrical Engineer
FDA-CDRH-ODE-DAGRID-GHDB



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Richard C. Chapman
Date: 2014.04.16
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/s/

PATRICIA J MADARA

04/22/2014

Signing in DARRTS for CDRH device evaluation reviewer, Sajjad Syed. Supervisory sign off by Richard Chapman

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206321 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: liraglutide Dosage Form: 3 mg / day Strengths: 6 mg / ml		
Applicant: NovoNordisk Agent for Applicant (if applicable):		
Date of Application: 12/20/13 Date of Receipt: 12/20/13 Date clock started after UN:		
PDUFA Goal Date: 10/20/14 (Monday)		Action Goal Date (if different):
Filing Date: 2/18/14		Date of Filing Meeting: 2/6/14
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 6		
Proposed indication(s)/Proposed change(s): indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m ² or greater (obese) or 27 kg/m ² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? XX	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 73206				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	XX		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>XX Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>XX Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p>XX</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	XX	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	XX	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? (<i>351(a)BLAs only</i>) <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	XX	<input type="checkbox"/>	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	<input type="checkbox"/> All paper (except for COL) XX All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment

If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	XX	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	XX	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	XX	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and	XX	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	XX	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."</i>	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	N/A; reviewed under the IND – no abuse potential
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	XX	<input type="checkbox"/>		
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	XX	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	XX	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	XX		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	XX	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	XX	<input type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	XX Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) XX Instructions for Use (IFU) XX Medication Guide (MedGuide) XX Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	XX	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	XX	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	N/A
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	XX		<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	XX		<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	XX		<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	XX	<input type="checkbox"/>	<input type="checkbox"/>	CDRH consults for HF study, device evaluation an inspection sent 1/3/14
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): 3/10/08	XX	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/10/13	XX	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		XX		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/6/2014

BLA/NDA/Supp #: NDA 206321

PROPRIETARY NAME: Saxenda

ESTABLISHED/PROPER NAME: liraglutide

DOSAGE FORM/STRENGTH: 3 mg injection

APPLICANT: NovoNordisk

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese) or 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea

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

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

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	
	CPMS/TL:	Julie Van der Vaag	
Cross-Discipline Team Leader (CDTL)	Eric Colman		
Clinical	Reviewer:	Julie Golden	
	TL:	Jim Smith	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NN	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NN	
	TL:		

Clinical Pharmacology	Reviewer:	Jaya Vaidyanathan	
	TL:	Immo Zadezensky	
Biostatistics	Reviewer:	Brad McEvoy	
	TL:	Mark Rothmann	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anthony Parola	
	TL:	Karen Davis Bruno	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NN	
	TL:		
Product Quality (CMC)	Reviewer:	Joe Leginus	
	TL:	Su Tran	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	
	TL:	Stephen Langille	
CMC Labeling Review	Reviewer:	NN	
	TL:		
Facility Review/Inspection	Reviewer:	Steve Hertz	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Vee	
	TL:	Yelena Maslov	

OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	
	TL:	Cynthia LaCivita	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	
	TL:	Janice Pohlman	
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:		
Other reviewers Biometrics VII (safety)	Rongmei Zhang / Janelle Charles / Mat Soukup		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>XX Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p>XX YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p>	<p><input type="checkbox"/> Not Applicable</p> <p>XX FILE</p>

<p>Comments: possible data integrity issues</p>	<input type="checkbox"/> REFUSE TO FILE XX Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	XX YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: late July 2014 <input type="checkbox"/> NO XX To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: reviewed by CSS, no abuse potential</p>	XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	XX Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: no filing issues</p>	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? XX YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO Comments:	
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) XX YES <input type="checkbox"/> NO Comments:	<input type="checkbox"/> Not Applicable

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>XX YES <input type="checkbox"/> NO</p> <p>XX YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>XX N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Eric Colman, M.D.; Deputy Director of DMEP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 28, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
XX	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. XX Review issues have been identified for the 74-day letter. List (optional): Clinical and Device related issues <u>Review Classification:</u> XX Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

PATRICIA J MADARA
03/28/2014