CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209803Orig1s000
209805Orig1s000
209806Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209803
	NDA 209806
PMR/PMC Set (####-#)	3311-1
Product Name:	Steglatro (ertugliflozin) tablets
	Segluromet (ertugliflozin and metformin hydrochloride) tablets
Applicant Name:	Merck Sharp & Dohme Corp.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, and pharmacokinetics (PK) of ertugliflozin as add-on to metformin background therapy for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 30-week double-blind, controlled extension. Patients will be randomized to receive one of two doses of ertugliflozin or placebo once daily. The ertugliflozin doses will be determined using a population PK model derived from the Phase 3 program (in adult subjects) for ertugliflozin. As part of the pediatric study, sparse blood samples for population PK and exposures-response analysis will be collected. An interim analysis of the PK data will be performed during this study to confirm acceptable exposure to ertugliflozin with the selected doses.

2. PMR/PMC Schedule Milestones[2, 3]

Final Protocol Submission:	10/2018
Study Completion:	03/2026
Final Report Submission:	09/2026

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The goal of this PMR is to establish the safety and efficacy of ertugliflozin in pediatric patients ages 10 to 17 (inclusive).

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☒ Yes

☐ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

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

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

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/s/

ELISABETH A HANAN
12/19/2017

MARY T THANH HAI
12/19/2017

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209803
PMR/PMC Set (####-#)	3311-2
Product Name:	Steglatro (ertugliflozin) tablets
Applicant Name:	Merck Sharp & Dohme Corp.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a randomized, double blind, placebo-controlled trial evaluating the effect of ertugliflozin on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with ertugliflozin to that observed in the placebo group is less than 1.3. This trial must also assess pregnancy outcomes and the following adverse events: amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersenstivity events, and malignancies. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess effects on renal function.

2. PMR/PMC Schedule Milestones[2, 3]

Final Protocol Submission:	not required because the trial is ongoing
Trial Completion:	10/2019
Final Report Submission:	12/2020

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

Patients with diabetes mellitus are at increased risk of cardiovascular events and cardiovascular death. As a result of concerns that some anti-diabetic drugs may actually increase the risk of cardiovascular events/death despite improving glycemic control, the development of new anti-diabetic agents has included an assessment of cardiovascular risk. An estimate of cardiovascular risk derived from a meta-analysis of cardiovascular data across the Phase 2 and 3 trials with ertugliflozin has provided sufficient evidence that ertugliflozin does not unacceptably increase cardiovascular risk above the pre-approval risk margin specified in the 2008 FDA Guidance to Industry, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." The Guidance also stipulates a more stringent risk margin would need to be demonstrated post-approval. This study is intended to fulfill that requirement by demonstrating that treatment with ertugliflozin does not result in an unacceptable increase in risk for major adverse cardiovascular events (MACE, i.e., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke).

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

Pregnancy outcomes and signals for amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, and malignancies will be further assessed in this trial.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select <u>one</u> explanation below.)

- ☐ <u>Subpart I or H (animal efficacy rule) PMR</u>: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ <u>Subpart H or E (accelerated approval) PMR</u>: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ <u>PREA PMR</u>: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***

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that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***

☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

☒ Longer-term data needed to further characterize the safety/efficacy of the drug

☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval

☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized

☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval

☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination

☐ Other reason (describe in text box below)

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]*****.** ***Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

☐ Assess a known serious risk related to the use of the drug

☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☒ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☒ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☒ Other

In general and at this time, observational studies, including an observational study using the ARIA system, are not considered sufficient to evaluate the cardiovascular endpoints of interest.

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

☒ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☒ Need to minimize bias and/or confounding via randomization
- ☒ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☒ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☒ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☒ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

   ☐ Yes
   ☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**
   [Select all that apply]

   ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
   ☐ Geriatric population
   ☐ Lactating/nursing mothers
   ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
   ☐ Orphan or rare disease population
   ☐ Pregnant women
   ☐ Racial/ethnic population
   ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

   ☒ The study/clinical trial meets criteria for a PMR or a PMC.

   ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

   ☒ The applicant has adequately justified the choice of milestone dates.

   ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ **(*If the PMR/PMC is a randomized controlled clinical trial*) The following ethical considerations were made with regard to:**

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

3. ☒ **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**.

Refer to electronic DARRTS signature

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

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/s/

ELISABETH A HANAN
12/19/2017

MARY T THANH HAI
12/19/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209806	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Segluromet Established/Proper Name: ertugliflozin and metformin hydrochloride Dosage Form: Tablets Strengths: ertugliflozin 2.5 mg/ metformin 500 mg; ertugliflozin 2.5 mg/ metformin 1000 mg; ertugliflozin 7.5 mg/ metformin 500 mg; ertugliflozin 7.5 mg/ metformin 1000 mg		
Applicant: Merck Sharp & Dohme Corp.		
Date of Receipt: December 19, 2016		
PDUFA Goal Date: December 19, 2017	Action Goal Date (if different):	
RPM: Elizabeth Godwin, DMEP		
Proposed Indication(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 020357 Glucophage (metformin hydrochloride) tablets	FDA's previous finding of safety and effectiveness (e.g., nonclinical, clinical, and metformin prescribing information)
Published literature	This original application relies upon published literature for changes to Section 8, Use in Specific Populations, in the Prescribing Information to comply with PLLR

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Two bioequivalence (BE) studies (Studies P027/1041 and P050/1058) were conducted in healthy subjects to bridge the highest (7.5 mg/1000 mg) and lowest (2.5 mg/500 mg) strengths of the ertugliflozin/metformin fixed combination drug product (FCDP) tablet and co-administration of individual components. Results of BE studies indicated that both of the highest and lowest strengths of the proposed ertugliflozin/metformin FCDP tablet are bioequivalent to co-administration of individual components, which was used in Phase 3 studies.

Regarding the other two strengths (7.5 mg/500 mg and 2.5 mg/1000 mg), the Sponsor has requested BE study waiver. The biowaiver was granted for the intermediate strengths as per 21 CFR 320.22(d)(2).

Study P027/1041, titled, "A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 7.5 mg/Metformin 1000 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects"

Study P050/1058, titled, "A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 2.5 mg/Metformin 500 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects"

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

Published Literature: According to the Pregnancy and Lactation Labeling Rule (PLLR), when human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s). Human data may come from the following sources: clinical trials, pregnancy exposure registries, other large scale epidemiologic/surveillance studies, and/or case series. The Agency has requested that an applicant complete a review of published literature, their pharmacovigilance database, and their pregnancy exposure registry (if applicable) to determine if there are new safety data that have become available, which warrant inclusion into labeling. In addition to the search of published literature conducted by the applicant, the Division of Pediatric and Maternal Health (DPMH) also conducts its own search of published literature. In the case of metformin, the applicant provided the Agency with 38 published articles and DPMH did not locate any new relevant information than what was submitted by the applicant. Based on the information from these 38 articles, DPMH was able to come up with an overall conclusion regarding the safe use of metformin during pregnancy. This process ensures that the safety information included in the newly PLLR converted labeling is accurate and up-to-date.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Glucophage (metformin hydrochloride) tablets	NDA 020357	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a fixed combination drug product (FCDP) of ertugliflozin and metformin hydrochloride.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

ELIZABETH R GODWIN
12/19/2017

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:	Deember 1, 2017
To:	Jean-Marc Guettier, M.D., Director 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)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Ramachandra, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SEGLUJAN (ertugliflozin and sitagliptin) SEGLUROMET **(**ertugliflozin and metformin**)**
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209805 NDA 209806
Applicant:	Merck & Co., Inc.

1 INTRODUCTION

On December 19, 2016, Merck & Co., Inc. submitted for the Agency's review a New Drug Application (NDA) for ertugliflozin and sitagliptin, tablets for oral use and ertugliflozin and metformin, tablets for oral use. Ertugliflozin and sitagliptin, tablets for oral use and ertugliflozin and metformin, tablets for oral use are indicated as an adjunct to diet and exercise to improve ghycemic 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 Metabolism and Endocrinology Products (DMEP) on December 21, 2016 for DMPP and OPDP to review the Applicant's proposed MG for ertugliflozin and sitagliptin, tablets for oral use and ertugliflozin and metformin, tablets for oral use.

2 MATERIAL REVIEWED

- Draft ertugliflozin and sitagliptin, tablets for oral use MG received on December 19, 2016 and received by DMPP and OPDP on November 24, 2017.
- Draft ertugliflozin and sitagliptin, tablets for oral use Prescribing Information (PI) received on December 19, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 24, 2017.
- Draft ertugliflozin and metformin, tablets for oral use MG received on December 19, 2016 and received by DMPP and OPDP on November 24, 2017.
- Draft ertugliflozin and metformin, tablets for oral use Prescribing Information (PI) received on December 19, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 24, 2017.
- Approved JARDIANCE (empagliflozin), tablets for oral use comparator labeling dated December 2, 2016.
- Approved INVOKANA (canagliflozin), tablets for oral use comparator labeling dated July 25, 2017.
- Approved FARXIGA (dapagliflozin), tablets for oral use comparator labeling dated October 20, 2017.
- Approved JANUVIA (sitagliptin), tablets for oral use comparator labeling dated August 10, 2017.
- Approved SYNJARDY (empafliglozin and metformin), tablets for oral use comparator labeling dated (b) (4).

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.

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.

In our collaborative review of the MGs we:

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

4 CONCLUSIONS

- The MGs 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 MGs 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 MGs.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/01/2017

MEENA RAMACHANDRA
12/01/2017

LASHAWN M GRIFFITHS
12/01/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 21, 2017

To: Elizabeth Godwin, Regulatory Project Manager, DMEP

Debra Beitzell, Labeling Development Team

From: Meena Ramachandra, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for ertugliflozin and sitagliptin; ertugliflozin and metformin

NDA: 209805; 209806

In response to DMEP's consult request dated December 21, 2016, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for the original NDA submissions for ertugliflozin plus sitagliptin and ertugliflozin plus metformin.

PI/Medication Guide: OPDP's comments on the proposed labeling are based on the draft PIs downloaded from the DMEP SharePoint site on November 20th and 21st. Per DMEP's request, OPDP's comments were uploaded to the SharePoint site and are also provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guides will be sent separately.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 11, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Ramachandra at (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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

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/s/

MEENA RAMACHANDRA
11/21/2017

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:	November 17, 2017
To:	Jean-Marc Guettier, M.D., Director 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)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Ramachandra, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	STEGLATRO (ertugliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209803
Applicant:	Merck & Co., Inc.

1 INTRODUCTION

On December 19, 2016, Merck & Co., Inc. submitted for the Agency's review a New Drug Application (NDA) for ertugliflozin, tablets for oral use. Ertugliflozin, tablets for oral use are indicated as an adjunct to diet and exercise to improve ghycemic control in adults with type 2 diabetes mellitus.

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- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

- The MG is 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 is 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.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/17/2017

MEENA RAMACHANDRA
11/17/2017

LASHAWN M GRIFFITHS
11/17/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 16, 2017

To: Elizabeth Godwin, Regulatory Project Manager, DMEP

Debra Beitzell, Associate Director for Labeling

From: Meena Ramachandra, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for Ertugliflozin

NDA: 209803

In response to DMEP's consult request dated December 21, 2016, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for the original NDA submission for ertugliflozin.

PI/Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP on November 2nd, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent separately.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 31, 2017 and September 11, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Ramachandra at (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/

MEENA RAMACHANDRA
11/16/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	October 27, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209803
Product Name and Strength:	Steglatro (ertugliflozin) tablets 5 mg, and 15 mg
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	July 31, 2017 and September 11, 2017
OSE RCM #:	2016-2925-1
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling for Steglatro (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Steglatro are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Ogbonna, C. Label and Labeling Review for Steglatro (NDA 209803). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 04. RCM No.: 2016-2925.

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/s/

CASMIR I OGBONNA
10/27/2017

HINA S MEHTA
11/01/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	October 27, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209805
Product Name and Strength:	Steglujan (ertugliflozin/sitagliptin) oral tablet Ertugliflozin 5 mg/sitagliptin 100 mg Ertugliflozin 15 mg/sitagliptin 100 mg (b) (4)
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	September 11, 2017
OSE RCM #:	2016-2928-01
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling for Steglujan (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Segluromet are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Ogbonna, C. Label and Labeling Review for Steglujan (NDA 209805). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 04. RCM No.: 2016-2928.

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/s/

CASMIR I OGBONNA
10/27/2017

HINA S MEHTA
11/01/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	October 27, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209806
Product Name and Strength:	Segluromet (ertugliflozin/metformin) oral tablet Ertugliflozin 2.5 mg / Metformin 500 mg Ertugliflozin 2.5 mg / Metformin 1000 mg Ertugliflozin 7.5 mg / Metformin 500 mg Ertugliflozin 7.5 mg / Metformin 1000 mg
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	September 11, 2017
OSE RCM #:	2016-2931-1
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling for Segluromet (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Segluromet are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Ogbonna, C. Label and Labeling Review for Segluromet (NDA 209806). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 04. RCM No.: 2016-2631.

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/s/

CASMIR I OGBONNA
10/27/2017

HINA S MEHTA
11/01/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: August 24, 2017 **Date consulted:** January 10, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

NDA/Drug: NDA 209803/TRADEMARK (ertugliflozin tablets)
NDA 209805/TRADEMARK (ertugliflozin/sitagliptin tablets)
NDA 209806/TRADEMARK (ertugliflozin/metformin tablets)

Applicant: Merck Sharp & Dohme Corporation

Subject: Pregnancy and Lactation Labeling

Proposed Indications:

Ertugliflozin

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Ertugliflozin/Sitagliptin

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate

Ertugliflozin/Metformin

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

Materials Reviewed:

- January 10, 2017, Maternal Health, DPMH consult, DARRTS Reference ID 4039152
- December 19, 2016, New NDAs, NDA 209803, 209805, 209806
- February 24, 2016, Submission to NDAs 209803, 209805 and 209806, containing PLLR literature search
- August 2, 2016, DPMH Review, Jane Liedtka, M.D., sitagliptin/metformin, NDA 21995; NDA 22044; NDA 202270
- May 9, 2016, DPMH Review Christos Mastroyannis, M.D., canagliflozin and metformin, NDA204353; NDA 205879
- March 18, 2016, DPMH Review Christos Mastroyannis, M.D., empagliflozin and metformin, NDA 206111

Consult Question: "Please confirm PLLR format is acceptable for labeling for all three products."

I**NTRODUCTION**

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of NDA 209803 (ertugliflozin); NDA 209805 (ertugliflozin/sitagliptin) and NDA 209806 ertugliflozin/metformin) labels.

REGULATORY HISTORY

On December 19, 2016, Merck submitted three original New Drug Applications (NDAs) for NDA 209806 for ertugliflozin tablets, NDA 209805 for ertugliflozin/sitagliptin tablets and NDA 209806 for ertugliflozin/metformin tablets to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Ertugliflozin
Ertugliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor and is currently not FDA approved.

Sitagliptin
Sitagliptin is a dipeptidyl peptidase-4 (DPP4) inhibitor that was originally approved on October 16, 2006, and is currently approved as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes.

Metformin
Metformin is a biguanide that was originally approved on March 3, 1995, and is currently approved as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes.

BACKGROUND

Drug Characteristics
Ertugliflozin Tablets for Oral Use
Ertugliflozin is an inhibitor of the sodium glucose co-transport 2 (SGLT2). SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. When SGLT2 is inhibited, renal reabsorption of filtered glucose is reduced and the renal threshold for glucose is lowered, thereby increasing urinary glucose excretion.

- Molecular Weight: 566 Daltons
- Plasma protein binding: 93.6%
- Mean systemic plasma clearance following IV 100 mcg dose: 11.2L/hr
- Mean elimination half-life in patients with normal renal function: 16.6 hours

Sitagliptin Tablets for Oral Use[1]
Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. Sitagliptin slows the inactivation of incretin hormones. Incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis and are released by the intestine throughout the day and increase in response to meals.

- Molecular Weight: 523.32 Daltons
- Peak plasma concentrations (mean T_{max}): 1 to 4 hours post dose
- Bioavailability: 87%
- 79% excreted unchanged in the urine
- Terminal $t_{1/2:}$ 12.4 hours following 100 mg oral dose

Metformin Tablets for Oral Use[2]
Metformin is a biguanide, which improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

- Molecular Weight: 165.63 Daltons
- Absolute bioavailability: 50% to 60%
- Elimination $t_{1/2:}$ 17.6 hours
- 90% renally eliminated

[1] 1.18.2017. FDA Approved Package Insert. Sitagliptin.
[2] 4.5.2017. FDA. Approved Package Insert. Metformin.

Diabetes Mellitus and Pregnancy[3]

Diabetes is the most common pregnancy complication occurring in approximately 4% of all pregnancies in the United States. Women with pregnancies complicated by diabetes mellitus may be separated into one of two groups: 1) Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy and 2) Pre-gestational diabetes (PGD): women known to have diabetes before pregnancy. The likelihood of developing GDM is significantly increased among certain subgroups. These include women with a family history of type 2 diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of major congenital malformations (MCM) has passed.[4]

Poorly controlled PGD increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, stillbirth and cesarean section (due to fetal macrosomia). In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression, and fetal complications, including macrosomia-related injuries (brachial plexus injury, hypoxia) and fetal hyperglycemia. Infants born to mothers with poorly controlled PGD are at an increased risk for hypoglycemia and respiratory distress. However, achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.[4,5,6]

Current State of the Labeling for Metformin

There are approximately 22 brand name products and dozens of generic products that contain metformin alone or metformin in combination. Some of the labels have been converted into the PLR/PLLR format and others have not. There is not a boxed warning for embryofetotoxicity or a contraindication for pregnancy or lactation. There are currently no contraception recommendations; however, the metformin containing products that have been PLLR converted have the following language in subsection **8.3 Females and Males of Reproductive Potential**, "Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women."

Current State of the Labeling for Sitagliptin

Sitagliptin and sitagliptin containing products are in the PLR format but not the PLLR format. DPMH provided PLLR recommended labeling recommendations August 2, 2016, for two sitagliptin containing products that have not yet been implemented. There is not a boxed warning for embryofetotoxicity or contraindication for pregnancy or lactation. Additionally, there are no pregnancy testing or contraception recommendations.

[3] August 2, 2016, DPMH Review, Jane Liedtka, M.D., Januvia (sitagliptin/metformin), NDA 21995; NDA 22044; NDA 202270

[4] Mills JL. Malformations in infants of diabetic mothers. Teratology. 1982:25;385-4.

[5] Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. Diabetes Med. 2014; 31(9): 1047-54.

[6] www.cdc.gov. Diabetes and Pregnancy. Accessed 8 August 2017.

REVIEW

PREGNANCY

Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors[7,8,9]
SGLT2 inhibitors prevent the resorption of glucose from the glomerular filtrate back into circulation and leads to an increase in urinary glucose excretion. There are no adequate or well-controlled studies with the SGLT2 inhibitors during pregnancy. Animal reproduction studies suggest SGLT2 inhibitors may affect renal development and maturation in rats when administered in late pregnancy (end of second trimester and third trimester). It is unknown if SGLT2 inhibitors are present in human milk. Animal reproduction studies have demonstrated that SGLT2 inhibitors are excreted in the milk of lactating rats. There is nothing known about the effects of SGLT2 inhibitors and fertility. There are no adverse effects on fertility with exposure to SGLT2 inhibitors in animals at doses below the maximum recommended human daily dose based on body surface area.

Ertugliflozin Tablets
Nonclinical Experience
Animal reproduction studies were not conducted with the combined products in TRADEMARK. The following data are based on studies conducted with the individual products.

In animal studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 17-times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin greater than 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature
Ertugliflozin is not an FDA approved product and there are currently no publications or pharmacovigilance data with regard to ertugliflozin and pregnancy.

Reports of Pregnancy from Ertugliflozin Clinical Development Program
There were two pregnancies in the ertugliflozin clinical development program. One pregnancy in the 5 mg group ended in an elective abortion. The other pregnancy was in the non-ertugliflozin group and resulted in a spontaneous abortion.

[7] May 9, 2016, DPMH Review Christos Mastroyannis, M.D., canagliflozin and metformin, NDA204353; NDA 205879
[8] March 18, 2016, DPMH Review Christos Mastroyannis, M.D., empagliflozin and metformin, NDA 206111
[9] Mosley J et al., 2015, Sodium-Glucose Linked Transporter 2 (SGLT2) Inhibitors in the Management Of Type-2 Diabetes: A Drug Class Overview, P&T, 40(7):451-462.

Sitagliptin Tablets

Nonclinical Experience

Sitagliptin tablets given orally at doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), (approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons) during organogenesis did not adversely affect development outcomes of either species. Placental transfer was approximately 45% at 2 hours and 80% at 24 hours (rats) and approximately 66% at 2 hours and 30% at 24 hours (rabbits).The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search using EMBASE and MEDLINE. Refer to the applicant's submission for specific search parameters.

The applicant submitted one article by Bellin (2017),[10] consisting of sitagliptin exposure during pregnancy. In this study, one patient was randomized to sitagliptin and was withdrawn from the study when pregnancy was reported. The subject delivered a healthy term infant. No further information was provided.

DPMH's Review of Literature

DPMH conducted a review of published literature using PubMed, EMBASE and Micromedex[11] and no information was found on sitagliptin exposure during pregnancy.

Metformin Tablets

Nonclinical Experience

No teratogenic effects were seen in rats and rabbits at doses 2 and 6 times the maximum recommended human daily dose based on body surface area, respectively. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search using EMBASE and MEDLINE. Refer to the applicant's submission for specific search parameters. The applicant located 38 articles describing exposure to metformin during pregnancy.

Case reports/Case series

Five case report/case series were identified describing metformin use during pregnancy demonstrating inconsistent findings with regard to adverse effects. See Table 1 submitted by the applicant in Appendix A for a summary of the referenced publications.[12,13,14,15,16] The

[10] Bellin et al., (2017), Sitagliptin treatment after total pancreatectomy with islet autotransplantation: a randomized, placebo controlled study, American Journal of Transplantation, 17:443-450.

[11] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9 August 2017.

[12] Nagai T, Negishi T, Imamura M et al. Metformin use in an obese diabetic patient from weeks 1 to 21 of pregnancy. Kitakanto Medical Journal 2005; 55 (1): 37-39.

[13] Ashraf S, Mazhar S, Masood H. Role of metformin in reducing frequency of 1st trimester miscarriage among pregnant women with polycystic ovarian syndrome at Nishtar Hospital Multan. Pakistan Journal of Medical and

summarized publications included one case report with a patient with type 2 diabetes and the remaining four publications included patients with polycystic ovarian syndrome (PCOS) only. Metformin is used off-label for the treatment of PCOS. No increase rates of miscarriage or congenital malformations were observed in the publications. One case of macrosomia was observed in one infant delivered at 37 weeks gestation to a 43 year old mother with type 2 diabetes. However, gestational diabetes, maternal obesity and maternal age are all positive risk factors for macrosomia.[17]

Observational Studies

The applicant reviewed 21 observational studies with regard to metformin exposure in pregnant women with gestational diabetes or type 2 diabetes (n=7), PCOS (n=13) and normoglycemic hyperinsulinemia (n=1). See Table 2 (study characteristics), Table 3 (obstetric outcomes) and Table 4 (neonatal outcomes) submitted by the applicant in Appendix A for a summary of the referenced publications.[18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38]

Health Sciences 2015; 9 (1): 179-81.

[14] Turner MJ, Walsh J, Byrne KM et al. Outcome of clinical pregnancies after ovulation induction using metformin. Journal of Obstetrics and Gynaecology 2006; 26 (3): 233-35.

[15] Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. Fertility and Sterility 2006; 85 (4): 1002-9.

[16] Palshetkar NP, Pai HD, Takhtani M et al. Metformin throughout pregnancy in women with polycystic ovary syndrome: Safety and advantages. International Journal of Infertility and Fetal Medicine 2011; 2(2): 61-64.

[17] Najafian M and M Cheraghi, Occurrence of Fetal Macrosomia Rate and It's Maternal and Neonatal Complications: A 5-year Cohort Study, International Scholarly Research Network Obstetrics and Gynecology, 2012:1-5.

[18] Balani J, Hyer SL, Rodin DA et al. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. Diabetic Medicine 2009; 26: 798-802.

[19] Coetzee EJ, Jackson WPU. Pregnancy in established non-insulin-dependent diabetics. A five-and-a-half year study at Groote Schuur Hospital. South African Medical Journal 1980; 58(20): 795-802.

[20] Gandhi P, Bustani R, Madhuvrata P et al. Introduction of metformin for gestational diabetes mellitus in clinical practice: has it had an impact? European Journal of Obstetrics & Gynecology and Reproductive Biology 2012; 160: 147-50.

[21] Goh JEL, Sadler L, Rowan J. Metformin for gestational diabetes in routine clinical practice. Diabetic Medicine 2011;28:1082-87.

[22] Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. Diabetic Medicine 2000;17:507-11.

[23] Rai L, Meenakshi D, Kamath A. Metformin - A convenient alternative to insulin for Indian women with diabetes in pregnancy. Indian Journal of Medical Sciences 2009;63(11):491-97.

[24] Tertti K, Ekblad U, Vahlberg T et al.. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. The Review of Diabetic Studies 2008;5(2):95-101.

[25] Abd El Hameed AA, Shreif HE, Mowafy HE. The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. Middle East Fertility Society Journal 2011;16(3):204-208.

[26] Al-Biate MAS. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. Taiwanese Journal of Obstetrics and Gynecology 2015;54(3):266-69.

[27] Begum MR, Khanam NN, Quadir E et al. Prevention of gestational diabetes mellitus by continuing metformin therapy throughout pregnancy in women with polycystic ovary syndrome. Journal of Obstetrics and Gynaecology Research 2009;35(2):282-86.

[28] Bolton S, Cleary B, Walsh J et al. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. European Journal of Pediatrics 2009; 168:203-206.

[29] De Leo V, Musacchio MC, Piomboni P et al. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. European Journal of Obstetrics Gynecology and

The number of metformin-exposed patients ranged from 30 to 465 throughout the published literature. Six cohort studies compared the effect of metformin compared to insulin treatment on obstetric and/or neonatal outcomes in women with gestational diabetes or type 2 diabetes. Thirteen cohort studies involved the use of metformin in women with PCOS around the time of conception and during pregnancy. Nine studies compared pregnancy outcomes in women with PCOS treated with metformin to those who either did not receive metformin or discontinued once pregnancy was identified. Three studies compared women with PCOS to healthy women without PCOS and one study compared current metformin exposed pregnancies to previous pregnancies not exposed.

The data do not indicated an increased risk of adverse maternal complications relative to comparison group. Many of the publications, specifically those used in women with PCOS found metformin use throughout pregnancy to be beneficial toward increasing the likelihood of a term delivery, reducing the risk of miscarriage and pregnancy complication such as hypertension of pre-eclampsia; however, one study found an increase in incidence of pre-eclampsia in metformin exposed women compared to insulin or sulfonylurea treated women. However, the study did not take into account confounding factors such as obesity, preexisting conditions or chronic kidney disease.

The data collected with regard to metformin and neonatal outcomes are limited by sample size; however, the data suggest that metformin use during pregnancy does not increase the risk of neonatal complications.

Reproductive Biology 2011;157(1):63-66.

[30] Glueck CJ, Wang P, Goldenberg N et al. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Human Reproduction 2002;17(11):2858-64.

[31] Glueck CJ, Goldenberg N, Pranikoff J et al. Effects of metformin-diet intervention before and throughout pregnancy on obstetric and neonatal outcomes in patients with polycystic ovary syndrome. Current Medical Research and Opinion 2013;29(1):55-62.

[32] Jakubowicz DJ, Iuorno MJ, Jakubowicz S et al. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism 2002;87(2):524-29.

[33] Khattab S, Mohsen IA, Aboul Foutouh I et al. Metformin reduces abortion in pregnant women with polycystic ovary syndrome. Gynecological Endocrinology 2006;22 (12):680-84.

[34] Khattab S, Mohsen IA, Aboul Foutouh I et al. Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with polycystic ovary syndrome? Prospective cohort study. Gynecological Endocrinology 2011;27 (10):789-93.

[35] Kovo M, Weissman A, Gur D et al. Neonatal outcome in polycystic ovarian syndrome patients treated with metformin during pregnancy. Journal of Maternal-Fetal and Neonatal Medicine 2006;19(7):415-19.

[36] Nawaz FH, Khalid R, Naru T et al. Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? Journal of Obstetrics and Gynaecology Research 2008;34 (5):832-37.

[37] Nawaz FH, Rizvi J. Continuation of metformin reduces early pregnancy loss in obese Pakistani women with polycystic ovarian syndrome. Gynecologic and Obstetric Investigation 2010;69(3):184-89.

[38] Todorova-Ananieva K, Konova E, Iafusco D et al. Pregnancy outcomes in normoglycemic women with hyperinsulinemia treated with metformin before and during pregnancy-a case-control study biguanid in pregnancy of hyperinsulinemic women. Acta Medica Bulgarica 2010;37(1):30-38.

Randomized clinical studies
The applicant identified 12 randomized clinical studies with regard to metformin exposure during pregnancy. See Table 5 in Appendix A for a summary of these publications as submitted by the applicant.[39,40,41,42,43,44,45,46,47,48,49,50] Nine of the studies include pregnant women with gestational diabetes or type 2 diabetes comparing metformin versus insulin for maternal or neonatal outcomes, one study reviewed the use of metformin compared to placebo in obese pregnant women without diabetes and two placebo-controlled trials describe the use of metformin in pregnant women with PCOS.

Metformin was not shown to be associated with differences in neonatal or maternal outcomes as compared to insulin. The same results were observed in the trials comparing metformin to placebo in women with PCOS.

DPMH's Review of Literature
DPMH conducted a review of available published literature using PubMed, EMBASE and Micromedex for relevant publications on the use of metformin exposure during pregnancy. No new relevant information was located in addition to what was submitted by the applicant.

Review of Applicant's Pharmacovigilance Database
The applicant performed a search of their pharmacovigilance database, Merck Adverse event Reporting and Review System (MARRS) for spontaneous reports of pregnancy for sitagliptin

[39] Refuerzo JS, Gowen R, Pedroza C et al. A pilot randomized, controlled trial of metformin versus insulin in women with type 2 diabetes mellitus during pregnancy. American Journal of Perinatology 2015:30(2):163-69.
[40] Ainuddin J, Karim N, Hasan AA et al. Metformin versus insulin treatment in gestational diabetes in a developing country: a randomized control trial. Diabetes Research and Clinical Practice 2015;107(2):290-99.
[41] Ainuddin JA, Karim N, Zaheer S et al. Metformin treatment in type 2 diabetes in pregnancy: An active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. Journal of Diabetes Research 2015;doi:10.1155/2015/325851.
[42] Ibrahim MI, Hamdy A, Shafik A et al. The role of adding metformin in insulin-resistant diabetic pregnant women: A randomized controlled trial. Archives of Gynecology and Obstetrics 2014;289(5):959-65.
[43] Waheed S, Malik FP, Azhar SB. Efficacy of metformin versus insulin in the management of pregnancy with diabetes. Journal of the College of Physicians and Surgeons Pakistan 2013;23(12):866-69.
[44] Mesdaghinia E, Samimi M, Homaei Z et al. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: A randomized blinded trial. International Journal of Preventive Medicine 2013;4(3):327-33.
[45] Hickman MA, McBride R, Boggess KA et al. Metformin compared with insulin in the treatment of pregnant women with overt diabetes: A randomized controlled trial. American Journal of Perinatology 2013;30(6):483-89.
[46] Rowan JA, Hague WM, Gao W et al. Metformin versus insulin for the treatment of gestational diabetes. New England Journal of Medicine 2008;358(19):2003-15.
[47] Moore LE, Briery CM, Clokey D et al. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. Journal of Reproductive Medicine 2007;52(11):1011-15.
[48] Chiswick C, Reynolds RM, Denison F et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. The Lancet Diabetes & Endocrinology 2015;3(10):778-86.
[49] Morin-Papunen L, Rantala AS, Unkila-Kallio L et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): A multicenter, double-blind, placebo-controlled randomized trial. Journal of Clinical Endocrinology and Metabolism 2012;97(5):1492-1500.
[50] Vanky E, Stridsklev S, Heimstad R et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: A randomized, controlled multicenter study.

and sitagliptin/metformin. A total of five reports were retrieved; however, each of the reports had insufficient information, including missing patient identifiers and pending outcomes.

In addition to the data retrieved from the MARRS database, the applicant also submitted a review of the 10th Annual Report on Exposure during Pregnancy from the Merck Pregnancy Surveillance Program (Previously called the Merck Pregnancy Registry for Januvia (sitagliptin) and Janumet (sitagliptin/metformin). See August 2, 2016, DPMH review by Jane Liedtka, M.D., of Januvia (sitagliptin) and Janumet (sitagliptin/metformin), NDA 21995; NDA 22044; NDA 202270 for a review of the available data from the pregnancy surveillance program from August 2006 to August 3, 2014.

The 10th annual report of the pregnancy surveillance program covers the time period August 2006 to August 3, 2016. Reports are classified as retrospective or prospective. The primary outcomes of interest are birth defects and pregnancy outcomes (live births, fetal deaths [nonviable pregnancies ≥ 20 weeks gestation], elective terminations and spontaneous abortions [spontaneous loss before the 20th week post-LMP]. Birth defects are classified according to the Center for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines.

From August 4, 2006 to August 3, 2016, the surveillance program has received 201 reports, and of these reports, 74 were from the United States and 127 were received internationally. Of the 74 US reports, 40 met enrollment criteria. Twenty-nine reports were prospective and 11 were retrospective. See Table 1 below for outcomes from prospective reports.

Table 1: Pregnancy Outcomes for all Enrolled, Prospective Reports*

(August 4, 2006 through August 3, 2016)

Report Type: Prospective	Total Women	Live Births	Spontaneous Abortions	Elective Abortions	Fetal Death	Lost to Follow-up	Pending
JANUVIA	20	11†	2	0	0	8	0
JANUMET	9	3	0	0	0	5	1
TOTAL	29	14†	2	0	0	13	1

† 1 twin pregnancy

*Table copied from applicant's submission

Of the 29 prospective reports, the following outcomes were reported:

- 13 have been lost to follow-up
- One report was pending at the time of submission
- 15 pregnancies resulted the following:
  - 14 live births (1 twin birth)
  - Two spontaneous abortions occurred in the first trimester of pregnancy to women taking sitagliptin

No congenital anomalies were reported. See Table 2 below for timing of exposure for pregnancies with known outcomes.

Table 2: Timing of Exposure for Enrolled, Prospective Reports with Known Outcomes*

(August 4, 2006 through August 3, 2016)

Outcome	Exposure in 1st trimester		Exposure in 2nd trimester		Exposure in 3rd trimester		Throughout pregnancy	
Product	Januvia	Janumet	Januvia	Janumet	Januvia	Janumet	Januvia	Janumet
Live Birth	4	3	0	0	3	0	2	1
Spontaneous abortions	2	0	0	0	0	0	0	0
Fetal Death	0	0	0	0	0	0	0	0
Elective Abortion	0	0	0	0	0	0	0	0
Total	6	3	0	0	3	0	2	1

*Table copied from applicant's submission

Of the 11 retrospective reports, the following outcomes were reported:

- One report resulting in a live birth was lost to follow-up
- One elective abortion
- Five spontaneous abortions
- Four live-births.

There were two congenital anomalies in the retrospective reports, and the following was reported:

- 30 year-old female, who was exposed to sitagliptin throughout pregnancy, delivered an infant with cleft lip and palate. No additional information was provided.
- A patient exposed to sitagliptin/metformin during pregnancy underwent an elective termination at 19 weeks gestation due to diagnosis of fetal encephalocele observed on prenatal ultrasound. No additional information was provided

Table 3: Pregnancy Outcomes for all Enrolled, Retrospective Reports*

(August 4, 2006 through August 3, 2016)

Report Type	Total Women	Live Births	Spontaneous Abortions	Elective Abortions	Fetal Death	Lost to Follow-up	Pending
JANUVIA	7	3	3	0	0	1	0
JANUMET	4	1	2	1	0	0	0
TOTAL	11	4	5	1	0	1	0

*Table copied from applicant's submission

Reviewer Comments:

- *There were no congenital anomalies observed among the enrolled, prospective reports in the pregnancy surveillance program. At this time there are insufficient data to make definitive conclusions about pregnancy outcomes and the likelihood of drug-associated risks.*
- *In an amendment to the NDAs on August 23, 2017, the applicant explained that the change in name of the Pregnancy Registry to the Merck Pregnancy Surveillance program in the "10th Annual Report on Exposure during Pregnancy from the Merck Pregnancy Surveillance Program (Previously called the Merck Pregnancy Registry for Januvia (sitagliptin) and Janumet (sitagliptin/metformin)," was merely a change in nomenclature and not a modification of program structure, scope, content or the process for data collection. Subsequent to this submission the applicant has decided to retain the original nomenclature of Pregnancy Registry.*

Summary of Pregnancy Data for Ertugliflozin, Sitagliptin and Metformin

Animal reproduction studies were conducted with the individual drug products and not in combination. Adverse renal changes were observed in rats with ertugliflozin administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 17-times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. No adverse developmental outcomes or teratogenic effects were observed in animal reproduction studies in sitagliptin or metformin.

Ertugliflozin is not an FDA approved product. At this time there are only two reports of ertugliflozin exposure during pregnancy from the clinical development program with one of the two pregnancies resulting in an elective termination.

Limited data from published literature with regard to sitagliptin and metformin exposure are not sufficient to demonstrate or rule-out a drug-associated risk to the fetus.

DPMH notes that poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications and the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

LACTATION

Ertugliflozin Tablets

Nonclinical Experience

Ertugliflozin is present in rat milk. The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on area-under-curve (AUC). There were adverse effects to developing kidneys (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations) of juvenile rats directly exposed to TRADEMARK during a developmental period corresponding to human kidney maturation. However, due to species-specific differences in lactation physiology, the clinical relevance of

these data is not clear. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature
Ertugliflozin is not an FDA approved product and there are currently no publications or pharmacovigilance data with regard to ertugliflozin and lactation.

Sitagliptin Tablets
Nonclinical Experience
Sitagliptin is present in rat milk at concentrations four-fold higher in maternal milk than plasma. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature
The applicant performed a search of published literature on sitagliptin exposure and lactation and no information was located.

DPMH conducted a search of *Medication and Mother's Milk*,[51] the Drugs and Lactation Database (LactMed),[52] Micromedex[11] and of published literature in PubMed and Embase. No information was found in LactMed or from published literature.

In *Medications and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that there "are no data available on the transfer of sitagliptin into human milk. Levels will probably be quite low due to its size and kinetics. Some caution is recommended until we have more data."[51]

Micromedex notes, "It is unknown whether sitagliptin is excreted into human milk. In lactating rats, sitagliptin is secreted into the milk at a plasma ratio of 4:1. Until further data are available, use caution when sitagliptin is administered to a nursing woman."[11]

Metformin Tablets
Nonclinical Experience
Metformin is present in rat milk at levels comparable to those in plasma. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature
The applicant conducted a literature search using EMBASE and MEDLINE. Refer to the applicant's submission for specific search parameters. No published literature was located with regard to metformin exposure during lactation.

[51] Hale, T. Medication's and Mothers Milk. Springer Publishing Company, 2017.
[52] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DPMH conducted a search of *Medication and Mother's Milk*,[51] the Drugs and Lactation Database (LactMed),[52] Micromedex[11] and of published literature in PubMed and Embase. No new information was located in PubMed or EMBASE.

Medications and Mother's Milk, LactMed and Micromedex all reference information from published literature that demonstrate metformin presence in human milk in low amounts. See summary below.

Gardner et al. (2003),[53] two small lactation studies were conducted to determine the milk-to-plasma ratio of metformin in lactating mothers and to estimate infant exposure. In study one, blood samples were taken from 2 infants for nursing mothers taking metformin 500 mg twice daily for diabetes throughout a dosing interval at steady state. In study two, five lactating healthy women who volunteered to express milk after weaning were given metformin, 500 mg during weaning and were studied for 72 hours. The milk-to-plasma ratios based on AUC in study one were 0.37, 0.50 and 0.71 and estimated infant dose 0.18%, 0.20% and 0.21% of the maternal dose. No adverse events were reported in the infants. Also, in study two, the milk-to-plasma ratio was unable to be calculated for three of the subjects. For the two subjects where the milk-to-plasma ratio was calculated were 0.27 and 0.27 and the infant doses 0.11% and 0.25%.

In another similar lactation study by Hale, et al.(2002)[54], seven women (ages 26- 38 years) who took metformin orally (median dose of 1500 mg daily) and their infants (5-25 months old) were studied. The mean milk-to-plasma ratio was 0.35 (range: 0.13 to 0.58). The mean relative infant dose was 0.28% (range: 0.15 to 0.42%) of the maternal weight-adjusted dosage. Based on maternal (n=4) and/or physician (n=2) observation, the infants appeared to be developing normally. In two infants, a Denver Developmental Screening test was done, which was normal. The developmental outcome for one infant was unknown.[3]

In lactation study, Briggs et al. (2005),[55] seven women were started on metformin 500mg twice daily right after their cesarean section. Two women were excluded from the study, and two other women stopped breastfeeding but continued to provide breastmilk samples. Serum and milk samples were collected from the mothers on postpartum days 4 and 17. Three infants had blood glucose levels drawn at the same time as maternal samples. The mean milk: serum ratio was 0.63 (range 0.36 to 1), and the relative infant dose was 0.65% (range 0.43 to 1.08%). In three infants, the blood glucose concentration after four hours of feeding was normal (47 to 77mg/dL). The mothers reported no side effects in the infants.[3]

The breastfed infants of mothers, who were taking metformin during lactation, developed normally and experienced no adverse effects. None of the infants studied had low blood glucose levels and their mothers reported no adverse reactions in the infants.[56] Metformin had no effect on duration of breastfeeding.[15,50]

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[53] Gardiner SJ et al., 2003, Transfer of metformin into human milk. Clinical Pharmacol Ther, 73(1):71-77.
[54] Hale TW, et al., 2002, Transfer of metformin into human milk, Diabetologia, 45(11):1509-1514.
[55] Briggs GG, et al., 2005, Excretion of metformin into breast milk and the effect on nursing infants, Obstet Gyncol, 105(6):1437-41.
[56] Glueck CJ et al., 2006, Growth, motor and social development in breast-and formula-fed infants of metformin-treated women with polycystic ovary syndrome, J Pediatr , 148:628-632.

Review of Applicant's Pharmacovigilance Database for Metformin and Sitagliptin
The applicant performed a search of their MARRS database for spontaneous reports of lactation and neonatal exposure through breastmilk of sitagliptin and metformin. No relevant cases were retrieved.

Summary of Lactation Data for Ertugliflozin, Sitagliptin and Metformin
Ertugliflozin, sitagliptin and metformin are all present in rat milk. There were adverse effects to developing kidneys (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations) of juvenile rats directly exposed to ertugliflozin during a developmental period corresponding to human kidney maturation.

There are no data on the presence of ertugliflozin or sitagliptin and human milk.

Metformin is present in human milk in low levels. Based on published literature, metformin has a milk-to-plasma ratio range from 0.13 to 1 and a relative infant dose range between 0.11 and 1%. A drug that has a milk-to-plasma ratio that is less than one is considered safe to use while breastfeeding. When the relative infant dose range is less than 10% of the maternal dose, the medication is considered safe for use during breastfeeding.[57] Based on published literature, metformin does not appear to have adverse effects on the breastfed infant; however, this information is limited due to small sample size.

Due to the potential for adverse effects on kidney development by ertugliflozin, DPMH agrees that the risk/benefit statement for subsection 8.2, Lactation will state the following;
"Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of TRADEMARK is not recommended while breastfeeding."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Ertugliflozin Tablets
Nonclinical Experience
No effects on fertility were observed in embryonic development studies with rats administered ertugliflozin at 386 times the maximum human recommended dose. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature
Ertugliflozin is not an FDA approved product and there are currently no publications or pharmacovigilance data with regard to ertugliflozin and females and males of reproductive potential.

Sitagliptin Tablets
Nonclinical Experience
No adverse effects were seen on fertility in rats dosed with oral sitagliptin at doses 12 times the maximum human recommended dose; however, at higher doses, non-dose related resorptions in females were observed at approximately 25 and 100 times the maximum recommended human

[57] Nice F and A Luo, 2012, Medications and breast-feeding: Current Concerts, Journal of American Pharmacists, 51(1):86-94.

dose. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature

The applicant performed a literature search with regard to sitagliptin and fertility and no publications were located. DPMH conducted a search of published literature using PubMed and EMBASE and one case report on sitagliptin and possible effects on spermatogenesis was located.

According to Hibi (2011),[58] a 39 year old physician with a history of Kawasaki's disease diagnosed at age five, diabetes and retrograde ejaculation due to diabetes. He was treated successfully with amoxapine and semen analysis demonstrated volume of 0.2 ml, sperm concentration of 213 X 106/ml and 53% motility. He began treatment with sitagliptin 50 mg per day and when the semen analysis was repeated it revealed no sperm. He discontinued the sitagliptin and semen analysis recovered revealing a volume of 0.3 ml, sperm concentration of 171 X 106/ml and 30% motility.

Metformin Tablets

Nonclinical Experience

In animal reproduction studies, fertility of male or female rats was unaffected by metformin exposure at doses 3 times the maximum recommended human dose based on body surface area. The reader is referred to the full Pharmacology/Toxicology review by Jessica Hawes, Ph.D., DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search using EMBASE and MEDLINE. Refer to the applicant's submission for specific search parameters. The applicant reviewed one case report and two randomized controlled trials with regard to metformin and its effect on fertility. The review of published literature is limited and resulted in inconsistent findings. In one case report by Ebrahimi (2014),[59] a female with polycystic ovary syndrome (PCOS) using metformin for ovulation induction resulted in an ovarian pregnancy and a serous cyst adenoma; however, it is unclear if the metformin use is related to the outcome.

In two randomized control trials by Legro, et al. (2007)[60] and Palomba, et al. (2011),[61] metformin was used in females with PCOS. In one study (Legro 2007), the results included lower ovulation in the metformin group compared to other drugs used in the study. In another study by Palomba (2011), metformin compared to placebo resulted in reduced ovarian reserve in patients being treated for *in vitro* fertilization. It is unclear whether metformin directly played a

[58] Hibi H et al., 2011, DPP-IV inhibitor may affect spermatogenesis, Diabetes Research and Clinical Practice, 93:e74-e75.

[59] Ebrahimi M, Akbari Asbagh F. Simultaneous serous cyst adenoma and ovarian pregnancy in an infertile woman. International Journal of Fertility and Sterility 2014;8(1):85-90.

[60] Legro RS, Barnhart H, Schlaff WD et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New England Journal of Medicine 2007;356(6):551-66.

[61] Palomba S, Falbo A, Di Cello A et al. Does metformin affect the ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve? A randomized controlled trial. Fertility and Sterility 2011;96(5):1128-33.

role in the fertility results as the Palomba study was limited to infertile PCOS patients with reduced ovarian reserve and concomitant medications, such as gonadotropins, were administered in the study.

DPMH's Review of Literature
In addition to the applicant's published literature search, DPMH also conducted a review of published literature using Embase and PubMed to evaluate the use of metformin and its effects on fertility.

According to Haas (2017),[62] metformin was previously a commonly prescribed medication for PCOS patients as part of fertility treatments; however, its use has declined as studies have demonstrated that there is no evidence that metformin improved live-birth rates.

The Cochrane Database of Systematic Reviews, Bordewijk, et al. (2017),[63] conducted a systematic review of five randomized controlled trials that compared metformin to placebo during ovulation induction with gonadotrophins in women with PCOS, and the authors concluded that metformin was associated with higher rates of live birth, ongoing pregnancy and clinical pregnancy; however, the authors concluded that the data quality was low. The data quality was considered low due to the following reasons: 1) only two of the trials provided data on the primary outcome of live-birth. Of the two trials, one of these studies was not blinded and did not describe method of randomization, 2) the sample size in all five trials was small. Three of the five studies had sample sizes less than 32. The authors noted that in order to have a power of 80% to detect a 10% difference in a control live-birth rate of 30 to 40%, the study would need to include 700 to 800 subjects.

Two additional reviews described in Cochrane evaluated the evidence for metformin plus gonadotrophins versus gonadotrophins alone in clomiphene resistant women with PCOS. The first study reviewed live-birth data from one trial only and concluded that there was no evidence of a difference between metformin plus gonadotrophins versus gonadotrophins. The second study had a similar conclusion.

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome – Part 2, Goodman et al. (2015),[64] state that "metformin may indirectly induce ovulation by reducing the concentration of circulating insulin, leading to normalization of the pulsatile production of GnRH and gonadotropins." However, the publication also points out that the occurrence of ovulation with the use of metformin in patients with PCOS may correlate with reduced weight loss and not the

[62] Haas J and Y Bentov, 2017, Should metformin be included in fertility treatment of PCOS patients? Medical Hypothesis, 100(2017): 54-58.
[63] Bordewijk EM et al., 2017 Metformin during ovulation induction with gonadotrophins followed by timed intercourse of intrauterine insemination for subfertility associated with polycystic ovarian syndrome (Review), Cochrane Database of Systematic Review, 1:1-36.
[64] Goodman N et al., 2015. The American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome – Part 2, Endocrine Practice, 21(12):1415-1426.

use of metformin as weight loss in patients with PCOS is also thought to help regulate menstrual cycles.

Summary of Females and Males of Reproductive Potential
There are no effects on fertility demonstrated in animal reproduction studies with ertugliflozin, sitagliptin or metformin.

One case report was located with regard to sitagliptin and its possible effects on spermatogenesis; however, a single case report is insufficient to determine the validity of these findings.

Limited published literature in humans do not demonstrate consistent findings with regard to metformin exposure and its effects on fertility. As discussed above, metformin was previously a commonly prescribed medication for PCOS patients as part of fertility treatments; however, published literature have demonstrated conflicting evidence that metformin increases ovulation and the potential for pregnancy.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential (ertugliflozin/metformin only) subsections of TRADEMARK (ertugliflozin), TRADEMARK (ertugliflozin/sitagliptin) and TRADEMARK (ertugliflozin/metformin) labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," and "Data" sections."
- **Females and Males of Reproductive Potential, Section 8.3** (ertugliflozin/metformin only)
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). Subsection 8.3 was populated for TRADEMARK (ertugliflozin/metformin) only. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling for TRADEMARK (Ertugliflozin tablets)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from ertugliflozin, TRADEMARK is not recommended during the second and third trimesters of pregnancy. The limited available data with TRADEMARK use during pregnancy are not sufficient to determine a drug associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. In animal studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 17-times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin greater than 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis *(see Data)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses

greater than or equal to 5 mg/kg (1317-fold human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1 month recovery period.

In embryo-fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were approximately 300-times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707-times clinical dose) and rabbits (833-fold the clinical dose) was associated with reduced fetal viability in both species, and a higher incidence of a visceral malformation (membranous ventricular septal defect) in rats.

In a pre- and postnatal development study in pregnant rats, ertugliflozin was administered from gestation day 6 through lactation day 21 (weaning). Decreased postnatal growth (weight gain) was observed at maternal doses of ≥100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

8.2 Lactation

Risk Summary

There is no information regarding the presence of TRADEMARK in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats. *(see Data)*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactation exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of TRADEMARK is not recommended while breastfeeding.

Data

The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on AUC. Juvenile rats directly exposed to TRADEMARK during a developmental period corresponding to human kidney maturation were associated with a risk to the developing kidney (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations).

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant patients of the potential risk to a fetus with treatment with TRADEMARK. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of TRADEMARK is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*.

DPMH Proposed Pregnancy and Lactation Labeling for TRADEMARK (Ertugliflozin/Sitagliptin tablets)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to sitagliptin during pregnancy. Health care providers are encouraged to report any prenatal exposure to TRADEMARK by calling the Pregnancy Registry at 1-800-986-8999.

Risk Summary

Based on animal data showing adverse renal effects, from ertugliflozin, TRADEMARK is not recommended during the second and third trimesters of pregnancy. The limited available data with ertugliflozin and sitagliptin use during pregnancy are not sufficient to determine a drug associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations).* In animal reproduction studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 17-times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin greater than 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis. In animal reproduction studies, no adverse developmental effects were observed with oral administration of sitagliptin to pregnant rats and rabbits at doses 12-times the human exposure a the maximum recommended human dose *(see Data).*

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly

controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Animal reproduction studies were not conducted with the combined products in TRADNAME. The following data are based on studies conducted with individual components.

Ertugliflozin

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses greater than or equal to 5 mg/kg (1317-fold human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1 month recovery period.

In embryo-fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were approximately 300-times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707-times clinical dose) and rabbits (833-fold the clinical dose) was associated with reduced fetal viability in both species, and a higher incidence of a visceral malformation (membranous ventricular septal defect) in rats.

In a pre- and postnatal development study in pregnant rats, ertugliflozin was administered from gestation day 6 through lactation day 21 (weaning). Decreased postnatal growth (weight gain) was observed at maternal doses of ≥100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

Sitagliptin

Sitagliptin administered to pregnant rats and rabbits from during organogenesis did not adversely affect development outcomes at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats during organogenesis decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours post-dose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

8.2 Lactation

Risk Summary

There is no information regarding the presence of TRADEMARK in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin and sitagliptin are present in the milk of lactating rats *(see Data)*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactation exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of TRADEMARK is not recommended while breastfeeding.

Data

Ertugliflozin

The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on AUC. Juvenile rats directly exposed to TRADEMARK during a developmental period corresponding to human kidney maturation were associated with a risk to the developing kidney (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations).

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant patients of the potential risk to a fetus with treatment with TRADEMARK. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant. Report any prenatal exposure to TRADEMARK by calling the Pregnancy Registry at 1-800-986-8999. *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of TRADEMARK is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*

DPMH Proposed Pregnancy and Lactation Labeling for TRADEMARK (Ertugliflozin/Metformin tablets)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- Lactation: Breastfeeding not recommended (8.2)
- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, from ertugliflozin, TRADEMARK is not recommended during the second and third trimesters of pregnancy. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data).* The limited available data with TRADEMARK in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations).* In animal reproduction studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 17-times the maximum clinical dose caused renal pelvic and tubule dilatations and renal mineralization that were not fully reversible. There was no evidence of fetal harm in rats or rabbits at exposures of ertugliflozin greater than 300 times higher than the maximal clinical dose of 15 mg/day when administered during organogenesis. In animal reproduction studies with metformin hydrochloride administered to pregnant rats and rabbits during organogenesis at 2- to 6-times, respectively, a clinical dose of 2000 mg, did not result in adverse development effects *(see Data).*

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Animal reproduction studies were not conducted with the combined products in TRADEMARK. The following data are based on studies conducted with the individual products.

Ertugliflozin

When ertugliflozin was orally administered to juvenile rats from PND 21 to PND 90, increased kidney weight, renal tubule and renal pelvis dilatation, and renal mineralization occurred at doses greater than or equal to 5 mg/kg (1317-fold human exposures, based on AUC). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development, and did not fully reverse within a 1 month recovery period.

In embryo-fetal development studies, ertugliflozin (50, 100 and 250 mg/kg/day) was administered orally to rats on gestation days 6 to 17 and to rabbits on gestation days 7 to 19. Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were approximately 300-times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC. A maternally toxic dose (250 mg/kg/day) in rats (707-times clinical dose) and rabbits (833-fold the clinical dose) was associated with reduced fetal viability in both species, and a higher incidence of a visceral malformation (membranous ventricular septal defect) in rats.

In a pre- and postnatal development study in pregnant rats, ertugliflozin was administered from gestation day 6 through lactation day 21 (weaning). Decreased postnatal growth (weight gain) was observed at maternal doses of ≥100 mg/kg/day (greater than or equal to 331 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC).

Metformin

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- to 6-times a human dose of 2000 mg based on body surface area (mg/m2) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of TRADEMARK in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats *(see Data).* Published studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight adjusted dosage and a

milk/plasma ratio ranging between 0.13 and 1 . There are no reports of adverse effects on breastfed infants exposed to metformin *(see Data).* Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactation exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of TRADEMARK is not recommended while breastfeeding.

Data

Ertugliflozin

The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on AUC. Juvenile rats directly exposed to TRADEMARK during a developmental period corresponding to human kidney maturation were associated with a risk to the developing kidney (persistent increased organ weight, renal mineralization, and renal pelvic and tubular dilatations).

Metformin

Published clinical lactation studies report that metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant patients of the potential risk to a fetus with treatment with TRADEMARK. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of TRADEMARK is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*

Pregnancy

Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations (8.3)]*.

Appendix A. Summary of Published Literature submitted by the Applicant (Tables below have been copies and pasted from the applicant's February 24, 2017, submission to the applications)

Table 1: Details of the five case reports/case series*

Author (year)	No. of Patients/ No. of Pregnancies	Age (years)	Study Population	Time Course of Metformin Therapy	Obstetric/Neonatal Outcomes	Author's Conclusions
Nagai (2005)[12]	1/1	43	T2DM	Pre-conception through 21 weeks gestation	A macrosomia delivery (4070 g) occurred in the 37th week.	Metformin use until the 21st week may have induced macrosomia.
Ashraf (2015)[13]	123/123	Not reported	PCOS with previous 1st trimester miscarriage	Pre-conception through 1st trimester	Of 123 pregnancies, 9.8% resulted in 1st trimester miscarriage, and the remaining pregnancies were successful through the 1st trimester.	This study showed that metformin reduced 1st trimester miscarriages to 9.8%. Prospective randomized controlled trials with sufficient numbers of patients are needed to provide robust evidence to recommend the continuous use of metformin during the 1st trimester in pregnant women with polycystic ovary syndrome.
Turner (2006)[14]	50/50	23-41	PCOS	Pre-conception through 1st trimester	Of 50 pregnancies, 7 resulted in a 1st trimester loss and 43 resulted in a live birth. There were no multiple pregnancies. There were no perinatal deaths, and no cases of neonatal hypoglycemia, neonatal seizures, or congenital malformations. There was one case of fetal hydrops associated with supraventricular tachycardia and one case of hereditary autoimmune thrombocytopenia. Three neonates weighed >4.5 kg and 4 neonates weighed ≤2.5 kg. Two women developed pre-eclampsia and 4 women developed hypertension only. The overall cesarean section rate was 37%.	This study found no evidence of any adverse clinical effects when metformin is continued in the 1st trimester in women with PCOS following ovulation induction. There was also no evidence of an increase in the rate of miscarriage or multiple pregnancy.

Author (year)	No. of Patients/ No. of Pregnancies	Age (years)	Study Population	Time Course of Metformin Therapy	Obstetric/Neonatal Outcomes	Author's Conclusions
Thatcher (2006)[15]	188/237	18-38	PCOS	Pre-conception with variable discontinuation (majority stopped at 8-12 weeks gestation)	Of 237 pregnancies with 254 fetuses (217 single, 17 twin, and 1 triplet), 171 (72%) resulted in live births, 62 (26%) resulted in 1st trimester loss, and 4 (2%) resulted in 3rd trimester loss. Of the 171 pregnancies (24% of these met criteria for gestational diabetes mellitus) that produced 184 live births, 78% resulted in term deliveries (>37 weeks gestation) and 22% resulted in preterm deliveries. Of the 184 live births, 4 infants (2.2%) were born with a congenital abnormality; 2 of these infants did not survive. Four (2.2%) infants were small for gestational age, 51 (28%) had macrosomia. Pregnancy-induced hypertension was reported in 14% of pregnancies resulting in live birth.	In summary, active intervention that universally included metformin in the months before pregnancy resulted in fewer spontaneous abortions in patients with PCOS. To date there have been no adverse fetal or neonatal effects associated with metformin use in pregnancy. Additional studies are needed to evaluate whether its use throughout pregnancy will lower pregnancy complication rates.
Palshetkar (2011)[16]	56/56	28 (median age)	PCOS	Pre-conception through end of pregnancy	First trimester abortion occurred in 7/56 women (11%). The incidence of multiple pregnancies (all twins) was 8/56 (12.5%); 7 of these occurred following in vitro fertilization/ intracytoplasmic sperm injection or artificial insemination. Preterm labor occurred in 5/56 (9%) pregnancies. None of the neonates had macrosomia. One neonate was diagnosed with tracheoesophageal fistula. Four (7%) women developed gestational diabetes mellitus and 8 (14%) women developed pregnancy-induced hypertension.	This study suggests that metformin not only helps women with PCOS conceive but also promotes prevention of spontaneous abortion and development of gestational diabetes in women with PCOS. Moreover, metformin is not shown to be teratogenic and does not affect neonatal development. However, the study was limited by the lack of a randomized double blind PCOS group on placebo therapy.

*Applicant's Table

Table 2. Characteristics of the twenty-one observational studies*

Author (year)	Country	Study Population	Sample Size	Age (years): Mean (SD)
Gestational diabetes (GDM) or Type 2 diabetes (T2DM)				
Balani (2009)[18]	UK	GDM	Metformin: 100 Insulin: 100	Metformin: 34 (5) Insulin: 34 (5)
Coetzee (1980)[19]	South Africa	T2DM	Metformin+diet: 22 Glibenclamide+diet: 14 Metformin+glibenclamide+ diet: 45 Insulin: 42 Diet only: 37 Untreated group: 11	Metformin+diet: 33 Glibenclamide+diet: 32 Metformin+glibenclamide+ diet: 33 Insulin: 32 Diet only: 31 Untreated group: 35
Gandhi (2012)[20]	UK	GDM	Metformin: 293 Non-metformin: 299	Metformin: 32 (6) Non-metformin: 33 (6)
Goh (2011)[21]	New Zealand	GDM	Metformin alone: 249 Metformin+insulin: 216 Insulin: 399 Diet: 371	Not reported
Hellmuth (2000)[22]	Denmark	GDM or T2DM	Metformin: 50 Sulfonylurea: 68 Insulin: 42	Metformin: 32 (21-46) SU: 28 (16-40) Insulin: 29 (20-45)
Rai (2009)[23]	India	GDM or T2DM	Metformin: 30 Insulin: 30	Metformin: 31 (4) Insulin: 31 (4)
Tertti (2008)[24]	Finland	GDM	Metformin: 45 Insulin: 45 Diet only: 83	Metformin: 33 (5) Insulin: 33 (5) Diet only: 32 (5)
Polycystic ovary syndrome (PCOS)				
Abd El Hameed (2011)[25]	Egypt	PCOS	Metformin: 31 Non-metformin: 26	Metformin: 30 (4) Non-metformin: 28 (4)

Author (year)	Country	Study Population	Sample Size	Age (years): Mean (SD)
Al-Biate (2013)[26]	UAE	PCOS	Metformin: 56 Non-metformin: 50	Metformin: 28 (2) Non-metformin: 29 (2)
Begum (2009)[27]	Bangladesh	PCOS	Metformin: 29 Non-metformin: 30	Metformin: 28 (3) Non-metformin: 26 (4)
Bolton (2009)[28]	Ireland	PCOS	Metformin: 66 Non-metformin: 66	Metformin: 32 (4) Non-metformin: 32 (4)
De Leo (2011)[29]	Italy	PCOS	Metformin: 98 Healthy women: 110	Metformin: 32 (6) Healthy women: 33 (5)
Glueck (2002)[30]	USA	PCOS	40 women with PCOS Currently on metformin: 46 pregnancies Previous non-metformin: 100 pregnancies	Not reported
Glueck (2013)[30]	USA	PCOS	Metformin: 76 Community control: 156	Metformin: 32 (5) Non-metformin: 30 (6)
Jakubowicz (2002)[32]	USA	PCOS	Metformin: 65 Non-metformin: 31	Metformin: 30 (4) Non-metformin: 30 (3)
Khattab (2006)[33]	Egypt	PCOS	Metformin: 120 Non-metformin: 80	Metformin: 27 (2) Non-metformin: 28 (2)
Khattab (2011)[34]	Egypt	PCOS	Metformin: 200 Non-metformin: 160	Metformin: 31 (2) Non-metformin: 32 (2)
Kovo (2006)[35]	Israel	PCOS	Metformin: 33 Healthy women: 66	Metformin: 30 (4) Non-metformin: 31 (4)
Nawaz (2008)[36]	Pakistan	PCOS	Metformin (4-16 weeks): 40 Metformin (to 32 weeks): 20 Metformin (to delivery): 45 Non-metformin: 32	Metformin (4-16 weeks): 28 (4) Metformin (to 32 weeks): 29 (3) Metformin (to delivery): 27 (4) Non-metformin: 30 (3)
Nawaz (2010)[37]	Pakistan	PCOS	Metformin: 119 Non-metformin: 78	Metformin: 29 (4) Non-metformin: 26 (5)
Normoglycemic hyperinsulinemia				

Author (year)	Country	Study Population	Sample Size	Age (years): Mean (SD)
Todorova- Ananieva (2010)[38]	Bulgaria	Hyperin- sulinemia	Metformin: 34 Non-metformin: 32	28.5 (23-34) for all study population, without significant difference between the two groups

*Applicant's Table

Table 3. Frequency of specific obstetric outcomes in pregnant women using metformin amoung the observational studies reviewed*

Author (year)	Study Groups	Miscarriage (spontaneous	Cesarean Section	Gestational Hypertensio	Pre-eclampsia
Gestational diabetes (GDM) or Type 2 diabetes (T2DM)					
Balani (2009)[18]	Metformin	0	48 (48%)	6 (6%)	2 (2%)
	Insulin	0	52 (52%)	7 (7%)	9 (9%)
Coetzee (1980)[19]	Metformin+diet	2 (9.1%)	Not reported	Not reported	Not reported
	Glibenclamide+diet	0	Not reported	Not reported	Not reported
	Metformin+glibenclamide+ diet	2 (4.4%)	Not reported	Not reported	Not reported
	Insulin	5 (11.9%)	Not reported	Not reported	Not reported
	Diet only	3 (8.1%)	Not reported	Not reported	Not reported
	Untreated group	0	Not reported	Not reported	Not reported
Gandhi (2012)[20]	Metformin	Not reported	OR=0.72 (95% CI=0.52-1.01)	OR=2.04 (95%	OR=1.54 (95% CI=0.43-5.52)
	Non-metformin	Not reported			
Goh (2011)[21]	Metformin alone	0	90 (36.2%)	15 (6.0%)	7 (2.8%)
	Metformin+insulin	1 (0.5%)	82 (38.0%)	22 (10.2%)	8 (3.7%)
	Insulin	4 (1.0%)	182 (45.6%)	21 (5.3%)	16 (4.0%)
	Diet	2 (0.5%)	126 (34.0%)	21 (5.7%)	14 (3.8%)
Hellmuth (2000)[22]	Metformin	Not reported	15 (30%)	0	16 (32%)
	Sulfonylurea	Not reported	19 (28%)	1 (1%)	5 (7%)
	Insulin	Not reported	16 (38%)	1 (2%)	4 (10%)
Rai (2009)[23]	Metformin	Not reported	No differences	Not reported	No differences

Author (year)	Study Groups	Miscarriage (spontaneous	Cesarean Section	Gestational Hypertensio	Pre-eclampsia
	Insulin	Not reported	between the two groups	Not reported	between the two groups
Tertti (2008)[24]	Metformin	0	14 (31.1%)	0	4 (8.9%)
	Insulin	0	10 (22.2%)	1 (2.2%)	4 (8.9%)
	Diet only	0	15 (18.1%)	3 (3.6%)	2 (2.4%)
Polycystic ovary syndrome (PCOS)					
Abd El Hameed (2011)[25]	Metformin	1 (3.2%)	Not reported	Not reported	1 (3.2%)
	Non-metformin	7 (26.9%)	Not reported	Not reported	2 (7.7%)
Al-Biate (2013)[26]	Metformin	5 (8.9%)	0	Not reported	Not reported
	Non-metformin	18 (36%)	0	Not reported	Not reported
Begum (2009)[27]	Metformin	1 (3.3%)	Not reported	Not reported	Not reported
	Non-metformin	1 (3.3%)	Not reported	Not reported	Not reported
Bolton (2009)[28]	Metformin	Not reported	63 (95.4%)	Not reported	Not reported
	Non-metformin	Not reported	64 (96.9%)	Not reported	Not reported
De Leo (2011)[29]	Metformin	9 (9.1%)	22 (22.4%)	0	0
	Healthy women	22 (20%)	Not reported	10 (10.4%)	3 (2.8%)
Glueck (2002)[30]	Metformin	12 (26%)	Not reported	Not reported	Not reported
	Non-metformin	62 (62%)	Not reported	Not reported	Not reported
Glueck (2013)[31]	Metformin	14 (18%)	Not reported	Not reported	6 (10%)
	Community control	0	Not reported	Not reported	5 (3%)
Jakubowicz (2002)[32]	Metformin	6 (8.8%)	Not reported	Not reported	Not reported
	Non-metformin	13 (41.9%)	Not reported	Not reported	Not reported
Khattab (2006)[33]	Metformin	14 (11.6%)	Not reported	Not reported	Not reported
	Non-metformin	29 (36.3%)	Not reported	Not reported	Not reported
Khattab (2011)[34]	Metformin	0	106 (53%)	6 (3%)	Not reported
	Non-metformin	0	96 (60%)	13 (8%)	Not reported
Kovo (2006)[35]	Metformin	0	11 (32.3%)	7 (21.2%)	Not reported
	Healthy women	0	15 (22.6%)	4 (6.1%)	Not reported

Author (year)	Study Groups	Miscarriage (spontaneous	Cesarean Section	Gestational Hypertensio	Pre-eclampsia
Nawaz (2008)[36]	Metformin (4-16 weeks)	8 (20%)	Not reported	14 (43.7%) (gestational hypertension + pre-eclampsia)	
	Metformin (to 32 weeks)	2 (10%)	Not reported	6 (33.3%) (gestational hypertension + pre-eclampsia)	
	Metformin (to delivery)	0	Not reported	6 (13.9%) (gestational hypertension + pre-eclampsia)	
	Non-metformin	6 (18.7%)	Not reported	8 (38.4%) (gestational hypertension + pre-eclampsia)	
Nawaz (2010)[37]	Metformin	9 (8.8%)	Not reported	19 (16.5%)	Not reported
	Non-metformin	23 (29.4%)	Not reported	35 (45%)	Not reported
Normoglycemic hyperinsulinemia					
Todorova-Ananieva (2010)[38]	Metformin	3 (8.8%)	Not reported	0	0
	Non-metformin	6 (18.8%)	Not reported	0	0

*Applicant's Table

OR=odds ratio; CI=confidence interval.

Table 4. Frequency of specified neonatal outcomes in pregnatn women using metformin among the 21 observational studies*

Author (year)	Study Groups	Congenital Malformation	Macrosomia	Large for Gestational Age Birth Weight	Shoulder Dystocia	Preterm Delivery (<37 weeks)	Respiratory Dysfunction Syndrome
Gestational diabetes (GDM) or Type 2 diabetes (T2DM)							
Balani (2009)[18]	Metformin	5 (5%)	11 (11%)	14 (14%)	2 (2%)	0	3 (3%)
	insulin	6 (6%)	14 (14%)	25 (25%)	1 (1%)	10 (10%)	3 (3%)
Coetzee (1980)[19]	Metformin+diet	Total of 9 infants with definite abnormalities, including 7 major and 2 minor	2 (10%)	3 (15%)	Not reported	Not reported	0
	Glibenclamide+diet		0	4 (27%)	Not reported	Not reported	1 (6.7%)
	Metformin+ glibenclamide+diet		2 (5.6%)	13 (33%)	Not reported	Not reported	3 (7.7%)
	Insulin		7 (20%)	16 (41%)	Not reported	Not reported	2 (5.1%)
	Diet only		7 (21%)	9 (27%)	Not reported	Not reported	3 (8.6%)
	Untreated group		3 (43%)	3 (45%)	Not reported	Not reported	0
Gandhi (2012)[20]	Metformin	0	24 (8.2%)	43 (14.8%)	OR=0.33 (95%	OR=1.01 (95%	Not reported

Author (year)	Study Groups	Congenital Malformation	Macrosomia	Large for Gestational Age Birth Weight	Shoulder Dystocia	Preterm Delivery (<37 weeks)	Respiratory Dysfunction Syndrome
	Non-metformin	0	43 (14.3%)	71 (23.7%)	CI=0.06-1.67)	CI=0.57-1.80)	Not reported
Goh (2011)[21]	Metformin alone	Not reported	Not reported	29 (11.5%)	Not reported	31 (12.3%)	2 (0.8%)
	Metformin+insulin	Not reported	Not reported	30 (13.8%)	Not reported	28 (12.8%)	7 (3.2%)
	Insulin	Not reported	Not reported	75 (18.5%)	Not reported	78 (19.2%)	5 (1.2%)
	Diet	1 (0.3%)	Not reported	47 (12.4%)	Not reported	46 (12.1%)	8 (2.1%)
Hellmuth (2000)[22]	Metformin	4 (8%)	Not reported	19 (38%)	Not reported	11(22%)	9 (20%)
	Sulfonylurea	2 (3%)	Not reported	20 (29%)	Not reported	14 (20%)	16 (23%)
	Insulin	5 (12%)	Not reported	19 (44%)	Not reported	11 (26%)	9 (21%)
Rai (2009)[23]	Metformin	2 (6.5%)	0	Not reported	1 (3.2%)	2 (6.5%)	Not reported
	Insulin	2 (6.7%)	0	Not reported	0	1 (3.3%)	Not reported
Tertti (2008)[24]	Metformin	1 (2.2%)	7 (15.6%)	Not reported	0	2 (4.4%)	0
	Insulin	0	10 (22.2%)	Not reported	0	5 (11.1%)	1 (2.2%)
	Diet only	0	10 (12.0%)	Not reported	0	6 (7.2%)	2 (2.4%)
Polycystic ovary syndrome (PCOS)							
Abd El Hameed (2011)[25]	Metformin	0	1 (3.2%)	Not reported	Not reported	1 (3.2%)	Not reported
	Non-metformin	1 (3.9%)	1 (3.9%)	Not reported	Not reported	2 (7.7%)	Not reported
Al-Biate (2013)[26]	Metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Non-metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Begum (2009)[27]	Metformin	0	0	Not reported	Not reported	2 (6.9%)	Not reported
	Non-metformin	0	4 (13.3%)	Not reported	Not reported	3 (10%)	Not reported
Bolton (2009)[28]	Metformin	2 (3.0%)	Not reported	6 (9.1%)	Not reported	8 (11.9%)	Not reported
	Non-metformin	1 (1.5%)	Not reported	10 (15.2%)	Not reported	10 (15.8%)	Not reported
De Leo (2011)[29]	Metformin	Not reported	Not reported	Not reported	Not reported	0	Not reported
	Healthy women	Not reported	Not reported	Not reported	Not reported	6 (6.2%)	Not reported
Glueck (2002)[30]	Metformin	0	Not reported	Not reported	Not reported	Not reported	Not reported
	Non-metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Glueck	Metformin	1 (1.3%)	10 (16%)	Not reported	Not reported	8 (13%)	Not reported

Author (year)	Study Groups	Congenital Malformation	Macrosomia	Large for Gestational Age Birth Weight	Shoulder Dystocia	Preterm Delivery (<37 weeks)	Respiratory Dysfunction Syndrome
(2013)[31]	Community control	0	19 (14%)	Not reported	Not reported	16 (11%)	Not reported
Jakubowicz (2002)[32]	Metformin	1 (1.6%)	Not reported	Not reported	Not reported	8 (12.9%)	Not reported
	Non-metformin	0	Not reported	Not reported	Not reported	6 (33.3%)	Not reported
Khattab (2006)[33]	Metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Non-metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Khattab (2011)[34]	Metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Non-metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Kovo (2006)[35]	Metformin	No differences between the two groups	Not reported	Not reported	Not reported	7 (21.2%)	Not reported
	Healthy women		Not reported	Not reported	Not reported	14 (21.2%)	Not reported
Nawaz (2008)[36]	Metformin (4-16 weeks)	1 (3.1%)	Not reported	Not reported	Not reported	8 (25%)	Not reported
	Metformin (to 32 weeks)	0	Not reported	Not reported	Not reported	5 (27%)	Not reported
	Metformin (to delivery)	0	Not reported	Not reported	Not reported	2 (4.8%)	Not reported
	Non-metformin	0	Not reported	Not reported	Not reported	5 (19.2%)	Not reported
Nawaz (2010)[37]	Metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Non-metformin	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Normoglycemic hyperinsulinemia							
Todorova-Ananieva (2010)[38]	Metformin	0	0	Not reported	Not reported	0	Not reported
	Non-metformin	0	0	Not reported	Not reported	0	Not reported

*Applicant's Table

OR=odds ratio; CI=confidence interval.

Table 5. Summary of twelve randomized controlled trials*

Author (year)	Study Treatment/ Population/ Sample size	Study Results	Conclusions
Refuerzo (2015)[39]	Metformin vs. insulin in pregnant women with T2DM N=19	There were similar rates of cesarean delivery, birth weights, neonatal intensive care unit (NICU) admissions, respiratory distress syndrome, and neonatal dextrose treatment between groups. There was one case of fetal macrosomia in the insulin group, and one case of shoulder dystocia in the metformin group.	Metformin was similar to insulin.
Ainuddin (2015)[40]	Metformin vs. metformin+insulin vs. insulin in women with GDM N=150	Maternal weight gain was less in the metformin- treated groups (9.8 ±. 1.5 kg [metformin alone] vs. 9.8 ± 1.4 kg [metformin plus insulin] vs. 12.5 ± 1.1 kg [insulin alone] p<0.000). Pre-eclampsia was significantly less common in metformin treated groups. There were no perinatal deaths in the study. Mean birth weight was significantly less in metformin- treated groups (3.4 ± 0.4 kg vs. 3.3 ± 0.5 kg vs. 3.7 ± 0.5 kg p<0.01). Less neonatal morbidity was observed in metformin-treated groups.	There was no evidence of increased risk in pregnancy outcomes in the metformin groups vs. the insulin-only group.
Ainuddin (2015)[41]	Metformin vs. insulin in T2DM in pregnancy N=206	Less maternal weight gain (p<0.001) and pregnancy-induced hypertension (p=0.029) were observed in the metformin group. Small for date babies were more common in the metformin group (p<0.01). Neonatal hypoglycemia and NICU stays >24 hours were less common in the metformin group (p<0.01).	Metformin was not worse than insulin in T2DM and pregnancy.
Ibrahim (2014)[42]	Addition of metformin vs. insulin intensification in pre-existing diabetes mellitus (DM) or GDM N=90	In the metformin group, 36.9 % of women reached proper glycemic control at a daily metformin dose of 1500 mg; 18 (39.2 %) at a daily dose of 2000 mg, while 11 (23.9 %) received metformin at a daily dose of 2000 mg without reaching proper glycemic control, and needed an insulin dose increase. . Metformin was associated with less maternal hypoglycemia and decreased incidence of neonatal hypoglycemia and NICU admissions.	Adding metformin may be an alternative to insulin intensification.
Waheed (2013)[43]	Metformin vs. insulin in pregnant women with diabetes N=68	Similar glycemic control was observed with metformin and insulin.	Similar glycemic control was observed with metformin and insulin.

Author (year)	Study Treatment/ Population/ Sample size	Study Results	Conclusions
Mesdagh- inia (2013)[44]	Metformin vs. insulin in pregnant women with GDM N=200	No significant statistical differences were observed between groups for pregnancy-induced hypertension, pre-eclampsia, birth weight, dystocia, first and fifth minute Apgar scores, neonatal sepsis, route of delivery, neonatal liver function tests, hypoglycemia, anomaly, and stillbirth. Hemoglobin A_{1c} (HbA_{1c}) at the end of pregnancy, maternal weight gain during pregnancy, and the occurrence of preterm labor, neonatal jaundice, respiratory distress, and hospitalization of infants were greater in the insulin group.	There was no evidence that metformin is worse than insulin.
Hickman (2013)[45]	Metformin vs. insulin in pregnant women with overt diabetes N=31	Glycemic control was similar with metformin and insulin, with less subjective hypoglycemia in the metformin group. There was a similar incidence of initial neonatal glucose, gestational age at delivery, infant body mass index (BMI), umbilical cord C-peptide, and infant birth weight in the two treatment groups. There were no stillbirths or major malformations in the study cohort, and no intrapartum complications such as shoulder dystocia or postpartum hemorrhage requiring transfusion. In the metformin group, one woman experienced 13-week intrauterine fetal demise, attributed to a large subchorionic hematoma noted on ultrasound at 12 weeks. Another woman delivered a large for gestational age infant with meconium-stained fluid after only attending four prenatal visits.	No clear differences were observed between metformin and insulin.
Rowan (2008)[46]	Metformin vs. insulin in pregnant women with GDM N=751	Of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. The rate of the primary composite outcome (neonatal hypoglycemia; respiratory distress; need for phototherapy; birth trauma, 5-minute Apgar score <7; prematurity) was 32.0% in the group assigned to metformin and 32.2% in the insulin group (relative risk, 0.99 [corrected]; 95% CI, 0.80 [corrected] to 1.23 [corrected]). More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%, $p<0.001$). The rates of other secondary outcomes did not differ significantly between the groups. There were no serious adverse events associated with use of metformin.	In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications compared with insulin.

Author (year)	Study Treatment/ Population/ Sample size	Study Results	Conclusions
Moore (2007)[47]	Metformin and insulin in pregnant women with GDM N=63	Mean (+/- SD) fasting and 2-hour postprandial blood glucose did not differ statistically between the 2 treatment groups. The difference in the rate of cesarean delivery was not statistically significant between the 2 groups (p=0.102). Neonatal statistics were also not different between the metformin and insulin groups for birth weight, Apgar score at 5 minutes, respiratory distress syndrome, hyperbilirubinemia, neonatal hypoglycemia and NICU admission (p=0.144-0.373).	No significant differences were observed between metformin and insulin.
Chiswick (2015)[48]	Metformin vs. placebo in obese pregnant women with normal glucose tolerance N=449	Mean birth weight was 3463 g (SD 660) in the placebo group and 3462 g (548) in the metformin group. The size of the estimated effect of metformin on the primary outcome (Z score corresponding to gestational age, parity, and sex-standardized birth weight percentile of live-born infants delivered at ≥24 weeks of gestation) was non-significant (adjusted mean difference -0.029, 95% CI -0.217 to 0.158; p=0.7597). The difference in the number of women reporting the combined adverse outcome of miscarriage, termination of pregnancy, stillbirth, or neonatal death in the metformin group (n=7) vs. the placebo group (n=2) was not significant (odds ratio 3.60, 95% CI 0.74-17.50; p=0.11).	Use of metformin in obese women with normal glucose tolerance was not supported.
Morin-Papunen (2012)[49]	Metformin vs. placebo in pregnant women with PCOS N=320	Miscarriage rates were low and similar in the two groups (metformin 15.2% vs. placebo 17.9%, p= 0.8). Intent-to-treat analysis showed that metformin significantly improved pregnancy rates (PR) and live birth rates (LBR) (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, p=0.006; LBR: 41.9 vs. 28.8%, p=0.014) and PR in obese women (49.0 vs. 31.4%, p=0.04), and there was a similar trend in non-obese (PR: 58.6 vs. 47.6%, p=0.09; LBR: 46.7 vs. 34.5%, p=0.09) and obese women with regard to LBR (35.7 vs. 21.9%, p=0.07).	Metformin may improve pregnancy and live birth rates vs. placebo in PCOS.

Author (year)	Study Treatment/ Population/ Sample size	Study Results	Conclusions
Vanky (2010)[50]	Metformin vs. placebo in pregnant women with PCOS N=257 women (274 singleton pregnancies)	Pre-eclampsia prevalence was 7.4% in the metformin group and 3.7% in the placebo group (3.7%; 95% CI, -1.7-9.2) (p=0.18). Preterm delivery prevalence was 3.7% in the metformin group and 8.2% in the placebo group (-4.4%; 95% CI, -10.1- 1.2) (p=0.12). Gestational diabetes mellitus prevalence was 17.6% in the metformin group and 16.9% in the placebo group (0.8%; 95% CI, -8.6- 10.2) (p=0.87). The composite primary endpoint (pre-eclampsia, preterm delivery, and GDM) prevalence was 25.9 and 24.4%, respectively (1.5%; 95% CI, -8.9-11.3) (p=0.78). Women in the metformin group gained less weight during pregnancy compared with those in the placebo group. There was no difference in fetal birth weight between the groups.	Metformin did not reduce pregnancy complications in PCOS patients.

*Applicant's Table

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/s/

CARRIE M CERESA
08/24/2017

MIRIAM C DINATALE
08/24/2017

LYNNE P YAO
08/25/2017

Clinical Inspection Summary

Date	8/18/2017
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader, for Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Frank Pucino, Pharm. D., M.P.H., Clinical Reviewer William Chong, M.D., Team Leader Elizabeth Godwin, MSHS, CCRP, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 209803, 209805, 209806
Applicant	Merck Sharp & Dohme Corp.
Drug	ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin HCl
NME (Yes/No)	Yes
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Treatment of type 2 diabetes mellitus
Consultation Request Date	1/25/2017
Summary Goal Date	10/24/2017; 8/19/2017 (preferable)
Action Goal Date	12/19/2017
PDUFA Date	12/19/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for these new drug applications (NDAs) consisted of five domestic and five foreign clinical sites representing a total of 18 study sites as well as the co-sponsor Pfizer and the contract research organization Covance. The inspection of one clinical investigator listed below revealed regulatory violations. The inspection of the co-sponsor also revealed regulatory violations. The inspection of the contract research organization and the remaining clinical investigators revealed no regulatory violations.

In general, based on the inspections of the nine clinical sites, the co-sponsor and the contract research organization, the inspectional findings support validity of data as reported by the sponsor under these NDAs.

The classification for Dr. Martinez is Voluntary Action Indicated (VAI). Although regulatory

violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for Drs. Adawi, Akright, De La Rosa, Fragoso, Goldhaber, Ilavska, Shoemaker, and Lozno is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Report (EIR) for Drs. Adawi, Akright, De La Rosa, Goldhaber, Ilavska, and Shoemaker was submitted for review. The full Establishment Inspection Report (EIR) for Drs. Fragoso and Lozno was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for the co-sponsor Pfizer is VAI because monitors did not always ensure protocol training required by the monitoring plan was completed by clinical investigators, sub-investigators, and study coordinators prior to their involvement in the study. Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. The full Establishment Inspection Report (EIR) was submitted for review.

The classification for the contract research organization Covance is NAI. Data from this firm are considered reliable based on the available information. The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

IND 106447 for ertugliflozin was submitted to the FDA by Pfizer, Inc. September 28, 2009 and transferred to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co Inc., (Merck) on June 21, 2013. Merck and Pfizer, as co-sponsors, are seeking approval of ertugliflozin (NDA 209803) and two fixed-dose combinations of ertugliflozin (ertugliflozin/sitagliptin [NDA 209805] and ertugliflozin/metformin [NDA 209806]) for the treatment of type 2 diabetes mellitus (T2DM). All are being co-developed by Pfizer and Merck with Merck serving as the regulatory sponsor.

Sitagliptin is the active component in the approved products Januvia® and Janumet®. Metformin (Glucophage® and available as a generic) is approved for use in the United States for the treatment of T2DM.

Inspections were requested for four studies that were still ongoing at the time of application submission.

- **P001/B1521016** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled

Clinical Trial to Evaluate the Efficacy and Safety of Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus with Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Background Antihyperglycemic Therapy

The study began December 3, 2013. The duration of the trial was up to 67 weeks, with a 52-week double-blind treatment period including a 26-week Phase A (Visit 4 to Visit 8) and a 26-week Phase B (Visit 8 to Visit 11). Last Subject Last Visit in Phase A was March 11, 2016. Database lock for Phase A was April 28, 2016. The trial was conducted in 13 countries at 121 trial centers. There were 1709 subjects screened and 468 subjects enrolled.

The primary glycemic efficacy endpoint was the change from baseline in hemoglobin A1c (HbA1c) at Week 26. A secondary glycemic efficacy endpoint was the change from baseline in fasting plasma glucose (FPG) at Week 26. Primary and secondary efficacy analyses as well as safety analyses for data collected through Week 26 were performed after the completion of Phase A. The sponsor and sponsor's designee were unblinded at the completion of Phase A. However, investigators and subjects remained blinded to study medication treatment assignment for the duration of the study.

- **MK-8835-003/B1521022 (P003/1022)** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control despite Diet and Exercise

The study began October 18, 2013. The duration of the trial was up to 65 weeks, including a double-blind, placebo-controlled treatment period (Phase A) followed by a 26-week active treatment period (Phase B). Last Subject Last Visit in Phase A was January 16, 2016. The study was conducted in seven countries at 71 sites. There were 1067 subjects screened and 461 subjects enrolled. Three subjects were identified who were randomized across two sites in this trial and other trials. Results from these subjects were excluded entirely from all efficacy and safety analyses, including disposition and demographic tabulations.

The primary glycemic efficacy endpoint was the change from baseline in HbA1c at Week 26. A secondary glycemic efficacy endpoint was the change from baseline in FPG at Week 26. Primary and secondary efficacy analyses as well as safety analyses for data collected through Week 26 were performed after the completion of Phase A. Subjects' treatment assignments were unblinded to limited team members at the completion of the 26-week Phase A portion of this study (defined as database lock) to permit authoring of the clinical study report (CSR). Personnel associated with the conduct of the study at the contract research organization (CRO) Parexel, as well as trial site personnel and subjects, remained blinded and were not to be unblinded until after the 26-week Phase B portion of the study completed.

- **P006/B1521015** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in the Treatment of Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin

Trial initiation was April 7, 2014. The double-blind treatment period was 52 weeks in duration and divided into two 26-week phases (Phase A and Phase B). Last Subject Last Visit for Phase A was November 18, 2015. The trial was conducted in 12 countries and 89 trial centers enrolled subjects. There were 987 subjects screened and 462 subjects randomized.

The primary glycemic efficacy endpoint was the change from baseline in HbA1c at Week 26. A secondary glycemic efficacy endpoint was the change from baseline in fasting plasma glucose at Week 26. Primary and secondary efficacy analyses as well as safety analyses for data collected through Week 26 were performed after the completion of Phase A. Subjects' treatment assignments were unblinded at the completion of the 26-week Phase A portion of this study (defined as database lock) to permit authoring of the CSR. The sponsor and sponsor's designee were unblinded at the completion of Phase A. Personnel associated with the conduct of the study at Covance, as well as trial site personnel and subjects, remained blinded and will not be unblinded until after the 26-week Phase B portion of this study has been completed.

- **P007/1017** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy

This was a 104-week, multi-center, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 78-week active-controlled treatment period (Phase B). First Subject First Visit was January 10, 2014. Last Subject Last Visit in Phase A was January 26, 2016. This study was conducted in 14 countries with enrollment at 103 sites. There were 1535 subjects screened and 621 subjects enrolled.

The primary glycemic efficacy endpoint was the change from baseline in HbA1c at Week 26. A secondary glycemic efficacy endpoint was the change from baseline in fasting plasma glucose at Week 26. In addition, this study assessed changes in bone mineral density (BMD) by DXA, and so provided information on the bone safety of ertugliflozin. Subjects' treatment assignments were unblinded to the sponsor at the completion of the 26-week Phase A portion of this study (defined as database lock) to permit authoring of the CSR. Personnel associated with the monitoring of the study at Parexel, as well as trial site personnel and subjects, remained blinded and were not to be unblinded until after the 78-week Phase B portion of this study completed.

Sites were chosen based on the Office of Scientific Investigations (OSI) Risk-Based Site Selection Tool (RBSST). Two to three sites were requested for each study. The US contributed less than 50% of the data for all four studies to be inspected so foreign sites were included. Most sites were chosen based on high ranking, enrollment in two or more of the four chosen trials, and no inspectional history. Dr. Garber/Site 1001 was chosen due to the history of GCP non-compliance.

III. RESULTS (by Site):

Name of CI/ Address	Protocol # and # of Subjects Randomized	Inspection Date	Classification
Faiad Adawi Derech HaRambam Zefat, 13100 Israel	P001 Site 1006 6 subjects P006 Site 1006 6 subjects P007 Site 1033 4 subjects	05/10 – 05/16/2017	No Action Indicated (NAI)
Adiv Goldhaber Shuali Clinic 8 Eliezer Yaffe Raanana, 43452 Israel	P001 Site 1008 5 subjects P006 Site 1008 5 subjects	05/21 – 05/24/2017	No Action Indicated (NAI)
Michaela Garber 26 Bialik Be'er Sheva, 84350 Israel	P001 Site 1001 8 subjects P007 Site 1047 2 subjects	05/03 – 05/08/2017	No Action Indicated (NAI)
Adriana A. Ilavská Gercenova 4/A Bratislava, 851 01 Slovakia	P006 Site 1257 5 subjects P007 Site 1200 9 subjects	06/05 – 06/14/2017	No Action Indicated (NAI)
Hernan Yupanqui Lozno Carrera 16 A # 79-33 Bogota, 110221 Columbia	P001 Site 704 8 subjects P006 Site 704 7 subjects	05/23 – 05/27/2017	No Action Indicated (NAI)*

Laura Akright 5000 Schertz Parkway , Suite 200 Schertz, TX 78154-1403	P003 Site 1078 16 subjects P007 Site 1111 16 subjects	06/05 – 06/09/2017	No Action Indicated (NAI)
Veronica Fragoso Texas Center for Drug Development 6550 Mapleridge Street , Suite 201 Houston, TX 77081	P003 Site 1116 15 subjects P007 Site 1193 11 subjects	05/15 – 05/19/2017	No Action Indicated (NAI)*
Raymond De La Rosa 225 Medical Center Drive Suite 305 Paducah, KY 42003-7914	P001 Site 4 12 subjects	05/22 – 05/26/2017	No Action Indicated (NAI)
Gilbert Martinez 14726 Ramona Avenue Suite 110 Chino, CA 91710	P006 Site 51 14 subjects	07/31 – 08/04/2017	Voluntary Action Indicated (VAI)*
James Shoemaker 77 W. Granada Blvd. Ormond Beach, FL 32174-6302	P003 Site 1042 22 subjects	06/05 – 06/08/2017	No Action Indicated (NAI)
Covance Inc. 206 Carnegie Center Princeton, NJ 08540	P001/1016 P006/1015	07/18 – 7/28/2017	No Action Indicated (NAI)*
Pfizer Inc. Eastern Point Road Groton, CT 06340-5157	P003/1022 P007/1017	06/19 – 06/28/2017	Voluntary Action Indicated (VAI)*

Key to Compliance 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 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Faiad Adawi/ P001 Site 1006/ P006 Site 1006/ P007 Site 1033

For P001, there were 11 subjects screened and six subjects enrolled into the study; four subjects completed the study; one subject withdrew consent from the study and the investigator discontinued another subject from the investigational product due to a decreasing estimated glomerular filtration rate (eGFR). There were six subject records reviewed. The close out visit for P001 was January 23, 2017.

For P006, there were nine subjects screened and six subjects enrolled into the study; six subjects completed the study. There were six subject records reviewed. The close out visit for P006 was August 11, 2016.

For P007, there were four subjects screened and four subjects enrolled into the study; three subjects completed the study; one subject discontinued. There were four subject records reviewed. The trial was still ongoing at the site.

The Ethics Committee of record for all three studies was the Ziv Medical Center Institutional Helsinki Committee. This was a foreign site not under IND.

The site is a hospital which maintains a medical staff, including other physicians who participated in the study as sub-investigators and research coordinators. The subjects' study records were compiled in binders. The files were organized and legible. Informed consent documents were written in Hebrew, Russian and Arabic. The case report forms (CRFs) were electronic and were supplied by US based contract CROs Covance for studies P001 and P006 and Parexel for study P007.

For all trials, it was confirmed that subjects met study eligibility criteria. Protocol-specified blinding/randomization procedures were followed. All subjects were randomized and stratified properly using an automated system. Dr. Adawi's site appeared to input the subject data appropriately into the Interactive Voice Response System (IVRS).

For all trials, there was no under-reporting of adverse events. There were no discrepancies noted between the source records and the sponsor data line listings.

Actual data verification for primary as well as secondary efficacy endpoints HbA1c and fasting blood glucose could not be performed using the sponsor data listings included with the application because the site was still blinded to the efficacy endpoint parameters for all three studies. As a result, the HbA1c and fasting blood glucose data results were not in the subject study folder and could not be verified. However, the FDA inspector confirmed that subject samples were submitted to the (b) (4) at Week 26 and the laboratory confirmed that the testing was performed. The FDA inspector randomly checked other laboratory results in the subject files and there were no discrepancies found.

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.

2. Adiv Goldhaber/ P001 Site 1008/ P006 Site 1008

For P001, there were five subjects screened and five subjects enrolled into the study; three subjects completed the study; two subjects discontinued (both subjects had their investigational product discontinued but were followed-up per protocol). There were five subject records reviewed. The close out visit for P001 was December 21, 2016.

For P006, there were seven subjects screened and five subjects enrolled into the study; four subjects completed the study; one subject discontinued. There were five subject records reviewed. The close out visit for P006 was August 3, 2016.

The Ethics Committee of record for both studies was the Institutional Helsinki Committee at the Meir Medical Center Kfar Saba, Israel. This was a foreign site not under IND.

The site is a community clinic which maintains a medical staff, including other physicians who participated in the study as subinvestigators and research coordinator. The subjects' study records were compiled in binders. The files were organized and legible. Informed consent documents were written in Hebrew. CRFs were electronic and were supplied by US based CRO Covance.

For both trials, it was confirmed that subjects met study eligibility criteria. Protocol-specified blinding/randomization procedures were followed. All subjects were randomized and stratified properly using an automated system. The site appeared to input the subject data appropriately into the IVRS.

For both trials, there was no under-reporting of adverse events. There were no discrepancies noted between the source records and the sponsor data line listings.

Actual data verification for primary as well as secondary efficacy endpoints HbA1c and fasting blood glucose could not be performed using the sponsor data listings included with the application because the site was blinded to the efficacy endpoint parameters. As a result, the HbA1c and fasting blood glucose data results were not in the subject study folder and could not be verified. However, the FDA inspector confirmed that subject samples were submitted to the (b) (4) at Week 26 and the laboratory confirmed that the testing was performed. The FDA inspector randomly checked other laboratory results in the subject files and there were no discrepancies found.

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.

3. Michaela Garber/ P001 Site 1001/ P007 Site 1047

For P001, there were 21 subjects screened and eight subjects enrolled into the study; six subjects completed the study. There were eight subject records reviewed. The close out

visit for P001 was January 31, 2017 and the ethics committee was notified on March 6, 2017.

For P007, there were five subjects screened and two subjects enrolled into the study; no subject completed the study. There were two subject records reviewed. Last patient's discontinuation visit was on Feb 2, 2016. There has been no closeout at this site yet.

The site is a group practice which maintains a medical staff, including other physicians who participated in the study as subinvestigators and research coordinators. The EC of record was the Helsinki Institutional Ethics Committee at the Meir Medical Center in Kfar Saba, Israel. The informed consent documents were written in Hebrew and Arabic. This was a foreign site not under IND.

The subjects' study records were compiled in binders. CRFs were electronic and were supplied by US based contract CROs Covance for study P001 and Parexel for study P007.

Source data was compared with CRFs and data points provided with the assignment. Review of the subjects' source records versus the sponsor data listings did not reveal any data discrepancy that were not previously noted by the monitor and resolved by the site.

The sponsor stated in the CSR that a compliance investigation was conducted to evaluate issues with source documentation for P001. The following issues were identified by the sponsor: untimely documentation by Investigator (observations not immediately recorded); deficiencies in the Investigator's performance relative to site management and inadequate oversight of study staff; possible risks of inappropriate interviewing leading to low adverse event (AE) reporting; low or no reporting of hypoglycemia due to subjects' illiteracy (investigator completed hypoglycemia logs for illiterate subjects from glucose meter memory). Subjects randomized at this site were allowed to continue participation. Data from subjects at this site were included in analyses.

During the inspection, Dr. Garber said she was not aware of any site specific non-compliances related to the two studies. She said study coordinators were responsible for entering subject data into the eCRF within five calendar days of collecting the data, as described in the Merck eCRF entry guideline. However, data entry normally occurred within two days of the patient visit. Related to the allegation of lack of oversight, Dr. Garber said that every Thursday she had a meeting with her staff to review patient files with sub-investigators and the study coordinator. Although this study had three sub-investigators, Dr. Garber was principally involved in the majority of the patient visits, therefore providing additional direct study oversight.

Dr. Garber confirmed that there were no AEs during phase A of P001. No AEs were noted in the source records. There were five AEs during phase B of the study (after 26 weeks) that were documented in the subject folders as well as the eCRF.

- Subject screening # 100100015, randomization # 104218 had two AEs reported including: vaginal candidiasis that was treated with a vaginal cream and microalbuminuria, a condition related to diabetes. Dr. Garber said that in both cases these AEs were considered not to be related to the study drug as documented in the patient file.

- Subject screening # 100100002, randomization # 103615 had diarrhea that Dr. Garber determined was not related to the study drug.
- Subject screening # 100100001, randomization # 102411 had cough that Dr. Garber determined was not related to the study drug.
- Subject screening # 100100004, randomization # 102417 had conjunctivitis that Dr. Garber determined was not related to the study drug.

Dr. Garber said there were no reports of hypoglycemia events in the eight randomized subjects. She said there were no patient complaints indicating hypoglycemia and there was no record of hypoglycemia in the memory of the glucose meter routinely used by study subjects. Also, subjects were tested for hypoglycemia at scheduled study visits and the central laboratory results reflected no hypoglycemic events. The site completed hypoglycemia logs for all subjects from the glucose meter memory.

Actual data verification for primary as well as secondary efficacy endpoints HbA1c and fasting blood glucose could not be performed using the sponsor data listings included with the application because the site was blinded to the efficacy endpoint parameters. As a result, the HbA1c and fasting blood glucose data results were not in the subject study folder and could not be verified. However, the FDA inspector confirmed that subject samples were submitted to the (b) (4) at Week 26 and the laboratory confirmed that the testing was performed. The FDA inspector randomly checked other laboratory results in the subject files and there were no discrepancies found.

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.

4. Adriana A. Ilavská/ P006 Site 1257/ P007 Site 1200

For P006, there were nine subjects screened and five subjects enrolled into the study; five subjects completed the study. There were five subject records reviewed.

For P007, there were 16 subjects screened and nine subjects enrolled into the study; seven subjects completed the study. One subject (Subject 1011/40176) was discontinued after development of a vaginal fungal infection and dyspepsia. The other subject (Subject 1015/10388) discontinued due to poor glycemic control and increasing problems with his prostate. There were nine subject records reviewed.

The subjects in the studies are all Dr. Ilavská's patients. Advertising for recruitment for clinical studies is not allowed in Slovakia.

Arrangements were made prior to the inspection for a free-lance translator who read the study documents and translated conversations during the inspection. The informed consents for both studies are written in Slovak.

There are two ethics committees that approve and oversee clinical studies in Slovakia. One is a local committee; there are several local committees in Bratislava. The other is a central committee (multi-centric) that issues approvals to multiple sites. The local ethics committee for Study 006 was Etická komisia, Bratislavského samosprávneho kraja, Sabinovaská ul.č.16, 820 05 Bratislava. The local committee for Study 007 was Etická komisia Košického samosprávneho kraja, Námestie Maratónu mieru 1, 042 66, Košice, Slovakia. The central committee for both studies was Multicentrická Etická komisia, Etická komisia Banskobystrického samprávneho kraja, Námestie SNP 23, 974 01 Banská, Bystrica, Slovenská republika, (Multicentre Ethics Committee, Ethics Committee of Banská Bystrica Self-Governing Region, Námestie SNP 23, 974 01 Banská Bystrica, Slovak Republic). The committees do not require continuing review.

The subjects' records were mostly in Slovak with some documents in English. Informed consents and visit notes were in Slovak. Visit notes were printed. There were also worksheets. Reports of results of clinical laboratory assessments from the central laboratories were in English.

For both studies, subjects met enrollment criteria. Subjects were correctly withdrawn from prior medications and rescue medications were issued and taken according to the protocol.

For both studies, review of the source documents and comparison with the data listings did not find any un-reported adverse events. There were no discrepancies found for the comparison of the clinical laboratory assessments that were unblinded. The bone scans for Study 007 were done at a nearby facility; these results were also blinded and it was documented that the scans had been conducted on the subjects and sent to the reader.

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.

5. Hernan Yupanqui Lozno/ P001 Site 704/ P006 Site 704

For P001, there were 25 subjects screened and eight subjects enrolled into the study; eight subjects completed the study. There were eight subject records reviewed.

For P006, there were 15 subjects screened and seven subjects enrolled into the study; six subjects completed the study. There were seven subject records reviewed.

All study records were available and legible. For both studies, source records were compared to sponsor data line listings and there were no discrepancies. There was no under-reporting of adverse events.

The clinical site is still blinded and did not have any laboratory results that could be verified against primary efficacy endpoints listed in the CSR. The FDA inspectors did confirm that the site did draw the required blood samples for the HbA1c and fasting plasma glucose at the appropriate time points.

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.

6. Laura Akright/ P003 Site 1078/ P007 Site 1111

For P003, there were 30 subjects screened and 16 subjects enrolled into the study; 14 subjects completed the study. There were 30 subject records reviewed.

For P007, there were 31 subjects screened and 16 subjects enrolled into the study; 14 subjects completed the study. There were 31 subject records reviewed.

NorthEast Clinical Research of San Antonio is a private clinic where all research takes place. Dr. Akright is contracted to conduct clinical studies. Dr. Laura Akright and Dr. Bruce Akright (subinvestigator) were out-of-town during the time of this inspection. The co-owner and Study Research Coordinator for both studies was the only study personnel interviewed.

(b) (4) was the IRB of record.

For both studies, source records were compared to sponsor data line listings. There were no discrepancies. There was no evidence of any under-reporting of AEs. Primary efficacy endpoint data was verifiable through documented laboratory blood draws and subject diaries. The site is still blinded to the actual laboratory results.

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.

7. Veronica Fragoso/ P003 Site 1116/ P007 Site 1193

For P003, there were 29 subjects screened and 15 subjects enrolled into the study; nine subjects completed the study; four subjects withdrew and two were lost to follow-up. There were 29 subject records reviewed.

For P007, there were 41 subjects screened and 11 subjects enrolled into the study; nine subjects completed the study. There were 41 subject records reviewed.

For both studies, subject binders were found to be organized and complete. Source records were compared to sponsor data line listings and there were no discrepancies. There was no under-reporting of adverse events. Primary efficacy endpoint data was verifiable through documented laboratory blood draws and subject diaries. The site is still blinded to the actual laboratory results.

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.

8. Raymond De La Rosa/ P001 Site 4

There were 32 subjects screened and 12 subjects enrolled into the study; five subjects completed the study. One subject withdrew due to an AE; four subjects withdrew their consent; one subject was withdrawn by the investigator; and one subject withdrew due to a hypoglycemic event. There were 22 subject records reviewed.

Dr. De La Rosa is a contracted employee of Four Rivers Clinical Research, Inc., a dedicated research facility since 1994 that contracts with various physicians to conduct the clinical studies. Dr. De La Rosa also has a private practice which was located on the 4th Floor of the building in which the study was conducted. Subjects were recruited from his practice and from advertisements.

The IRB of record is (b) (4)

All source documents were maintained on site. A review of the source documents found them to be well organized and tabulated by study visit. The source documents were in good condition, complete and legible. Source records were compared to sponsor data line listings and there were no discrepancies. For the primary efficacy endpoint, as the site was blinded, it was confirmed that laboratory testing was performed.

There was no under-reporting of adverse events. A memo dated 31 August 2015 was sent to the Investigators from the Sponsor regarding the assessment of hypoglycemic events (both symptomatic and asymptomatic) and instructed them on how they should be reported. A Note to File dated September 9, 2015 indicated that the site reported all hypoglycemic events as an adverse event. This was a miscommunication during the Site Initiation meeting. The FDA inspector reviewed all Hypoglycemia Assessment forms for all enrolled subjects and all events were accounted for in both the eCRF and the sponsor 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.

9. Gilbert Martinez/ P006 Site 51

There were 40 subjects screened and 14 subjects enrolled into the study; nine subjects completed the study. There were 14 subject records reviewed.

The IRB of record was (b) (4). The study closed at the site October 11, 2016.

There has not been a final closeout visit.

The study records were organized, legible and available. Source documents were compared to the sponsor data line listings and there were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was not verifiable due to the site still being blinded. It was confirmed that laboratory testing was performed at the designated study visits.

During the inspection, it was noted that there were instances in which subjects were asked to return to the clinic for an additional blood draw due to either errors made by the study team on the lab requisition forms or improper storing of samples. Dr. Martinez does not have a dedicated freezer or refrigerator for storing samples as the study team indicated that all samples are shipped after collection.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for an investigation that was not conducted in accordance with the investigational plan. Specifically,

- Subjects who were on metformin ≥1500 mg/day and sitagliptin 100 mg/day for ≥8 weeks and who meet all other enrollment criteria were directly enrolled into the 2-week, single-blind, placebo run-in period at a combined Visit 2/3.
    - Subject 051-00003 (randomization # 600007 to placebo) and Subject 051-00029 (randomization # 600044 to ertugliflozin 15 mg) were enrolled into the trial while reporting <8 weeks on stable medication.
- Subjects who did not meet initial entry criteria but were within one of four groups of criteria at Visit 1/Screening were eligible to enter a wash-off/titration/dose-stabilization period beginning at Visit 2 and scheduled for Visit 3/Week -2
    - Subject 051-00010 (randomization # 600013 to ertugliflozin 5 mg) was on metformin only and did not meet any of the inclusion criteria for the wash-off/ titration/dose-stabilization period.

OSI Review Comment: The observations above were noted by the site monitor and reported as protocol deviations. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

Dr. Martinez confirmed that he would be responding to the findings in a written reply, which is still pending.

10. James Shoemaker/ P003 Site 1042

There were 41 subjects screened and 22 subjects enrolled into the study; 20 subjects completed the study. One subject withdrew consent after seven weeks (randomization # 0311470) and a second was dropped from dosing at 16 weeks but remained enrolled for follow up (randomization # 0311349). There were 16 subject records reviewed.

The central IRB providing oversight for the inspected trial was (b) (4)

(b) (4). The study was closed with the IRB on 11/17/16. There has not been a final closeout visit.

Dr. Shoemaker is the current owner of Ormond Medical Arts Family Practice and Ormond Medical Arts - Pharmaceutical Research Center. The research center is located adjacent to the family and internal medicine clinic. The clinic was established in 1950 and Dr. Shoemaker joined the practice in 1973. All subjects are referred from the clinic practice or by word of mouth.

The site maintains all study records in paper format. Records were noted to be complete, legible and well-organized. Original paper records were available for all study activities and printed certified copies of electronic medical records were available to support eligibility. Source records were compared to the sponsor data line listings and there were no discrepancies.

Most efficacy endpoints involved blinded laboratory data and thus were not verifiable during this establishment inspection. Secondary endpoints related to body weight and blood pressure changes were verified against the site-supplied case report form data. Adverse events and concomitant medications were verified against line listings through Week 26 and against case report forms for the full 52 weeks. There was no evidence of under-reporting of adverse events.

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.

11. Covance Inc./ P001/B1521016 and P006/B1521015

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO and deviations related to key safety and efficacy endpoints.

All monitoring reports for the sites noted above were inspected. In addition, monitoring reports of sites that underwent a directed audit and those noted for non-compliance were reviewed:

- P001 Dr. Lucas / Site 003
- P006 Dr Ramussen / Site 0073
- P006 Dr. Marquez / Site 1071 (disqualified as a PI for another study)
- P006 Dr. Tuomilehto / Site 1903

The visit reports in the clinical trial management system (CTMS) are electronically signed; however, these will not be fully transferred in the eTMF to the sponsor at the end of the

study. The CRO staff stated that metadata electronic signatures are held in the Covance database only and will not be provided to the sponsor at the end of the trial. However, it was pointed out by the FDA inspector that the signature certificates should be included in the eTMF as required by their TMF index requirements.

There were also several issues covered for both studies:

- The CSR for P001 states 22.6% of subjects in the trial were not stratified properly. Covance staff stated that a limited list of terms was provided in the protocol. Upon review of a complete list of medical history terms prior to Phase A database lock, additional CV disease and heart failure terms were identified in the eCRF system InForm. These were not consistent with the reported stratum in IVRS so these patients were then considered improperly stratified.
- The CSR for P001 states that there were subjects who enrolled multiple times. A Covance investigation found approximately 40 subjects who tried to enroll in multiple sites within a 50 mile radius in Florida only. Covance looked at sites in Texas and California who were in a 50 mile radius and found no multiple enrollees. The 40 subjects were excluded from all analysis populations in the CSR. Tabulations of study disposition and AEs were provided separately for these subjects in the CSR. Covance found the IRT system (Merck hired IRT CRO) could not distinguish the same subjects since it only retrieved month and year of the subject's date of birth (DOB). Covance looked at the full DOB, subject initials, and gender to reconcile the subjects and found the 40 subjects. Covance halted the randomization for the sites and only enrolled subjects once confirmed they were not duplicate subjects. A listing of the sites and subjects who had multiple enrollments was provided.
- A listing of Merck and Covance personnel was provided for both studies. It was confirmed that the personnel who worked primarily on the CSR involving Phase A will not be working on the actual study for Phase B. For example, the medical monitor unblinded for the CSR will not be used for Phase B monitoring.
- For P001, there were 78 subjects found that had at least one sample positive for metformin (PK and FBR) where metformin was not allowed as background therapy. Merck found a decrease in A1C between week 18 and 26 in the placebo arm. An analysis was conducted and found 78 subjects were positive for metformin. A list of the 78 subjects was provided. Since this was found after the database lock, they will include the 78 subject as a major protocol deviation (use of prohibited medication) in the Phase B protocol deviation listing.
- There were two subjects in Protocol 006 (Subjects 30 and 72) who had family history provided but were improperly consented to provide the information. Covance reported that it was standard language from Merck up until July 17, 2014. After this date, anyone randomized did not have the language in their consent. Early in the study about 10 subjects were randomized with this language, but only two subjects were affected and the information was collected. However, subsequently, the subjects signed consent which allowed for family history information. Copies of these informed consent forms were provided.

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

12. Pfizer Inc./ Sponsor P003/B1521022 and P007/B1521017

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

Study files were reviewed for 14 sites:

- Study P007/1017 sites 1033, 1047, 1200, 1111, 1193, 1109, 1115
- Study P003/1022 sites 1078, 1116, 1042, 1091, 1032, 1063, 1089

Ertugliflozin is being co-developed by Merck and Pfizer. The group responsible for making decisions regarding program wide issues regarding clinical aspects, manufacturing, and budgetary issues is the Joint Steering Committee (JSC). The Collaboration Agreement between Merck and Pfizer established the composition, responsibilities, and decision making procedures of the JSC. The Development Plan attached to the Collaboration Agreement between Pfizer and Merck established a single program wide Data Monitoring Committee (DMC) to be responsible for safety oversight for all the Core Phase III Clinical Trials.

Four of the studies were executed by Pfizer and five by Merck.

Pfizer led studies	Merck led studies
P003/B1521022	P001/B1521016
P004/B1521021	P002/B1521013
P007/B1521017	P005/B1521019
P012/B1521045	P006/B1521015
P017/B1521047	

It was confirmed that Merck and Pfizer Quality Assurance departments hold monthly meetings to discuss any ongoing or potential issues. Issues discovered by either firm's QA classified as significant are sent to a Cross Functional Team comprised of multiple departments/teams as needed. Oversight monitoring and escalation of issues was timely, appropriate, and with documentation.

A table of data cutoff dates, data extraction dates, data transfers to Covance, dates of cover pages of blinded data for the closed DMC meetings, and dates of the DMC meetings was prepared for the

inspection. The FDA inspector compared data extraction dates with screen shots of data file properties and confirmed they were created on the same dates.

PARAXEL was selected by Pfizer as CRO of the Pfizer led studies. PARAXEL QC checklists for blinded and unblinded data for Studies P003 and P007 which included checks of raw data updates, analysis data sets, and table listing and figures outputs were reviewed. The Closed Report cover sheet prepared by the un-blinded statistician for closed DMC sessions, DMC meeting minutes, and emails confirming the transfer of data from PARAXEL to Covance for DMC review were reviewed for every DMC meeting. There were no issues with transfer of files and the data packages for DMC review.

For the two adjudication committees that were led by Pfizer, Pfizer selected the chairs and members and shared the qualifications with Merck. Pfizer and Merck signatory approval for the members was provided by both firms' Clinical and Statistical Leads on the Pfizer led committee charters. Pfizer performed the same diligence checks on adjudication committee members as for the DMC members. It was confirmed that all activities of the committees were performed according to the charters.

The Unblinding Plans (Addendum to the SAP) for Studies P003/1022 and P007/1017 were reviewed. At the end of Phase A, PARAXEL programmers and statisticians would unblind the data and provide it to the Pfizer statistician. The remainder of the PARAXEL staff remained blinded at this point. The Pfizer statistician would then confirm the treatment codes were applied correctly to the database. The topline report does not contain the treatment codes. It contains only high-level (summary) results. This report would be shared with the Merck counterparts. The PARAXEL programmers and statisticians produced the final tables for inclusion within the CSR. The tables and listings were shared with Pfizer statisticians, clinicians, programmers, writers, supply chain, and regulatory for preparation of the draft study report. This was reviewed within Pfizer and by Merck representatives.

A list of all Pfizer and PARAXEL employees unblinded at the end of Phase A, a list of all Merck employees unblinded after Phase A and before final database lock, and a list of all Pfizer reviewers of Merck CSRs were reviewed and collected. While the un-blinding plans for both P007/1022 and P003/1017 have a statement that "limited Sponsor personnel have access to treatment assignments during Phase B" and "pre-specified individuals in senior management at both Pfizer and Merck" would be un-blinded at the summary level for review of the tables, listings, and figures (TLFs) and CSR, all individuals included on the lists of un-blinded personnel provided during the inspection had access to all tables and subject listings, including the senior management referred to in the unblinding plan. Pfizer staff stated the intent was to maintain the blind for all clinical investigators, subjects, and PARAXEL personnel performing site monitoring duties. This is consistent with the CSR and other sections of the Statistical Analysis Plan, which state "Phase B will remain blinded to subjects, investigators and members of the Parexel team performing site monitoring duties, with respect to individual subject treatment assignment".

The final CSR for P007 was stored in a document management system with restricted access. At the time the final CSR for P003 was produced, the study was complete and it was not necessary to restrict access.

Terminated site files were assessed during the inspection. Monitoring and escalation of events appeared to be handled in a timely manner:

- For Site 1089 (Dr. Brian Robert Tulloch) in Study P003/1022, during monthly review of clinical data the clinician discovered issues with washout of medication (Subject 0310382 randomized to ertugliflozin 15 mg improperly; did not meet criteria). The site was put on enrollment hold, retrained, and an oversight visit was conducted by Pfizer. When enrollment was re-opened, a different major protocol deviation was discovered during a routine monitoring visit and a decision was made to terminate the site (Subject 0310688 randomized to 5 mg ertugliflozin improperly; did not meet criteria). The site was notified of the decision to terminate on Dec 8, 2014. The subjects were given the opportunity to transfer to another site but opted out of the study as early discontinuations. All data from the three enrolled subjects was included in the CSR. Merck was notified of the termination through email and Merck notified FDA through a letter dated Dec 15, 2014.
- For Site 1115 (Dr. Jaime Sandoval) in Study P007/ 1017, the monitor performed a routine monitoring visit April 14-15, 2014 and Pfizer performed an oversite visit on April 21, 2014 (requested by the Study Team); there were numerous protocol deviations. Deviations included four subjects who signed the wrong version of ICF, one laboratory test which was repeated for a value that should have been a hard screen failure, and for five subjects the site did not comply with the screening visits (combined S2/S3 visit was separated). Merck was notified of the decision to terminate the site on April 21, 2014 and the site was notified on April 24, 2014. The five subjects active in screening at the time were marked as screen failures. Eight subjects in total were screened and none were randomized. During the inspection, there was documented email communication to Merck and Merck notification to FDA in a letter dated Nov 2, 2016.

According to information provided by Merck during this inspection, on March 13, 2015, PARAXEL received a data package from Covance which included the protocol number, site number, subject initials, DOB, gender, screening date, and randomization date, if applicable, of subjects involved in multiple screenings. An additional email from PARAXEL requested subjects' height and weight. PARAXEL then ran a check for gender, birthdate, height, and weight against information provided in the data package. This comparison was performed manually. The data package contained 269 subject enrollment records and included 39 subjects who were randomized at more than one site in either the same or more than one Merck ertugliflozin study. The analysis was run against all potential duplicate screenings. Confirmation of the potential duplicates was made through follow up at the clinical sites.

After recruitment was complete in the Pfizer program in June 2015, a programmatic check of gender, birthdate, height, weight, and region was performed by Pfizer for all subjects enrolled within the Pfizer studies and completed Oct 1, 2015.

As a result of these two analyses and through confirmation at the clinical sites, it was determined that seven individuals (representing 12 subjects) were randomized in more than one Pfizer study and/or Pfizer site: three subjects randomized in P003, four subjects enrolled in P007, and five subjects enrolled in P004. The data from these 12 subjects were considered compromised and not usable; all are excluded from all Pfizer safety and efficacy analyses.

A comparative analysis was not run between all subjects screened in the Pfizer led studies and all subjects screened in the Merck led studies. The only demographic information shared with PARAXEL/Pfizer was of the potential duplicate screenings in the Merck studies. Any subject who screened at only one Merck site and one Pfizer site would not have been identified by the analyses. They did not run a comparison between all Merck and Pfizer subjects as there was a higher likelihood of finding duplicate subjects in the Pfizer study subjects among the known multi-enrollers in the Merck studies.

The information provided to PARAXEL on March 13, 2015 contained 39 subjects who were randomized at more than one site in either the same or more than one Merck ertugliflozin study. After sharing the list, Covance identified an additional subject who was randomized at multiple sites (for a total of 40 subjects) and two additional subjects who were randomized once and attempted to enroll at second sites.

For future studies, each trial is required to complete an Integrated Quality Management Plan (IQMP) which now includes a question specific to risk of multi-site/multi-study enrollment. If the trial is at risk, a mitigation plan is required. Strategies that are included in the mitigation plan can be unique to the particular study. A control at the site level can be implemented through use of the Pfizer IVRS to identify multi-enrollers at each site. At the study level, a data review can be performed on IVRS and EDC data across sites within the same study.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to ensure proper monitoring. Specifically, monitors did not always ensure protocol training required by the monitoring plan was completed by clinical investigators, sub-investigators, and study coordinators prior to their involvement in the study. Additionally, clinical site staff missing required protocol training were not always identified and investigated in a timely manner. This was observed for eight out of the 14 clinical sites reviewed during this inspection.

OSI Reviewer Comment: Pfizer submitted a written response to the finding on July 20, 2017 with corrective and prevention actions that were deemed acceptable. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this sponsor appear acceptable.

{See appended electronic signature page}

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

CONCURRENCE: *{See appended electronic signature page}*

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/s/

CYNTHIA F KLEPPINGER
08/18/2017

JANICE K POHLMAN
08/18/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	209803
Brand Name	-
Generic Name	Ertugliflozin (Mk-8835/PF-04971729)
Sponsor	Merck Sharp & Dohme Corp.
Indication	Treatment of type 2 diabetes mellitus (T2DM)
Dosage Form	Tablets
Drug Class	Sodium-Glucose co-Transporter 2 (SGLT2) inhibitor
Therapeutic Dosing Regimen	5 mg once daily starting dose; up to 15 mg once daily as highest dose
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	300 mg (single dose), 100 mg qd (up to 14 days), and 25 mg qd (up to 12 weeks)
Submission Number and Date	001 / 12/19/2016
Review Division	DMEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of ertugliflozin 100 mg was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

This was a Phase 1, single-dose, randomized, 3-treatment, 6-sequence, 3-period crossover, placebo- and active-controlled study, 42 subjects received ertugliflozin 100 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs of ΔΔQTcF corresponding to the Largest Upper Bound for Ertugliflozin 100 mg and the Largest Lower Bound for Moxifloxacin
(FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Ertugliflozin 100 mg	24	3.0	(0.5, 5.5)
Moxifloxacin 400 mg*	3	14.9	(12.4, 17.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 11.5 ms.

The ertugliflozin geometric mean C_{max} at the supratherapeutic 100 mg ertugliflozin dose (1735 ng/mL) was ~6.5 times the mean steady-state C_{max} following highest proposed dose of 15 mg qd dose under fasted state (268.2 ng/mL). Amongst the potential worst case scenarios, the subjects with mild, moderate and severe renal impairment had mean increases in AUC_{inf} of ≤1.7-fold, and no clinically meaningful increases in C_{max}. Regarding the interaction with a UGT inhibitor (mefenamic acid), based on PBPK modeling, the predicted ertugliflozin AUC and C_{max} ratio (ertugliflozin + mefenamic acid/ertugliflozin alone) were 1.51 and 1.19, respectively. Thus, the exposures with the supratherapeutic dose of 100 mg adequately cover potential highest clinically relevant exposure scenario due to the effects of intrinsic/extrinsic factors with therapeutic dose.

2 PROPOSED LABEL

The sponsor included following QT-related language in their current proposed label.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of TRADEMARK on the QTc interval was evaluated in a Phase 1 randomized, placebo- and positive-controlled 3-period crossover study in 42 healthy subjects. At 6.5-fold of the therapeutic exposures with maximum recommended dose, TRADEMARK does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Ertugliflozin is an oral, selective inhibitor of sodium glucose co-transporter-2 (SGLT2) which inhibits renal glucose reabsorption and results in urinary glucose excretion (UGE) and reductions in plasma glucose and hemoglobin A1c (A1C) in patients with type 2 diabetes mellitus (T2DM). It possesses a high selectivity for SGLT2 versus SGLT1 and other glucose transporters (GLUT1-4). Ertugliflozin is being developed as an adjunct to diet and exercise for the treatment of T2DM.

Ertugliflozin and two fixed-dose combinations (FDCs) of ertugliflozin, with sitagliptin and with immediate release metformin, are being co-developed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), and Pfizer Inc, with Merck serving as the regulatory sponsor. The two FDCs combine anti-hyperglycemic agents (AHA) with complementary mechanisms of action to improve glycemic control in patients with T2DM. Registration of ertugliflozin (NDA 209803), ertugliflozin/sitagliptin (NDA 209805) and ertugliflozin/metformin (NDA 209806) for the treatment of T2DM are being pursued concurrently.

3.2 MARKET APPROVAL STATUS

Ertugliflozin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From the IB (April 2011):

At concentrations of 30, 100, and 300 μM, PF-04971729 produced 2.9%, 8.3%, and 33.5% inhibition of the hERG current amplitude, respectively, with a calculated IC50 of >300 μM (129 μg/mL), which is ~ 19300-fold the predicted human unbound Cmax (0.00670 μg/mL) at the proposed Phase 3 dose of 10 mg once daily.

In the in vivo cardiovascular assessment, in addition to vehicle, ertugliflozin was administered to Beagle dogs as single doses of 1, 5, and 50 mg/kg in a cross-over design. During the 23-hour postdose observation period, there were no treatment-related effects on any hemodynamic, electrocardiographic (ECG), myocardial contractility, or activity parameters at 1 and 5 mg/kg. At 50 mg/kg, moderate and transient effects were observed, including a decrease in corrected QT interval (QTc, 6 msec) and a decrease of 489 mmHg/sec in left ventricular contractility with a concomitant increase in PR interval (4 msec) near Tmax (3.5 hours). An increase in systolic blood pressure (6 mmHg), and decrease in heart rate (6 bpm) commenced 8 hours postdose. All parameters returned to control values after 24 hours. At the no observed adverse event level (NOAEL) of 5 mg/kg, the unbound plasma exposure was approximately 6-fold greater than the predicted human unbound Cmax,ss of 0.0101 μg/mL at the highest Phase 3 dose of 15 mg once daily.

3.4 PREVIOUS CLINICAL EXPERIENCE

Sponsor reports that pooled 12-lead ECG data from the two Phase 1 dose escalation studies where single oral doses up to 300 mg and multiple doses up to 100 mg once daily

for 2 weeks were administered to 64 subjects did not reveal QTcF prolongation. No AEs of concern as per ICH E14 Guidance were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ertugliflozin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 106,447. The sponsor submitted the study report MK-8835-010-01/B1521025 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Placebo-and Active-Controlled Crossover Study to Determine the Effect of Single-Dose Ertugliflozin on the QTc Interval in Healthy Volunteers

4.2.2 Protocol Number

MK-8835-010-01/B1521025

4.2.3 Study Dates

Study Initiation Date: 06 November 2013
Study Completion Date: 25 August 2014

4.2.4 Objectives

Primary Objective: To demonstrate a lack of effect of ertugliflozin on the QTc interval relative to time-matched placebo in healthy volunteers.

Secondary Objectives:

- To determine study sensitivity by comparing the effect of moxifloxacin 400 mg on QTc interval relative to time-matched placebo.
- To evaluate the pharmacokinetics (PK) of ertugliflozin.
- To evaluate the safety and tolerability of a single oral dose of ertugliflozin 100 mg in healthy volunteers.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-dose, randomized, 3-treatment, 6-sequence, 3-period crossover (balanced Williams Square design), placebo- and active-controlled study conducted in 42 adult healthy male or female volunteers.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Subject- and investigator-blinded (sponsor open) with respect to ertugliflozin and placebo administration only. Administration of moxifloxacin was in an open-label manner to the subjects and investigators.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 3 treatments: ertugliflozin 100 mg, matching placebo for ertugliflozin, and moxifloxacin 400 mg.

4.2.6.2 Sponsor's Justification for Doses

Subjects will receive a single supratherapeutic dose of 100 mg ertugliflozin which is approximately 6.7 times the highest dose in the Phase 3 clinical program (ie, 15 mg). A C_{max} value of approximately1600 ng/mL is expected for the 100 mg single dose administered as tablets under fasted conditions in this study based on data derived from Study B1521001 (assuming linear kinetics and similar bioavailability between solution/suspension and tablet formulations).

The predicted supratherapeutic exposure of ertugliflozin 100 mg administered as a single dose in the fasted state (approximately 1600 ng/mL) ranges from approximately 5- to 10 times the mean expected steady state C_{max} following once daily administration of the therapeutic dose of 15 mg ertugliflozin administered in either the fasted (anticipated $C_{max,ss}$ approximately 300 ng/mL) or fed (anticipated $C_{max,ss}$ approximately 157 ng/mL) states, respectively.

Based on the multiple metabolic pathways for ertugliflozin, drug interactions between ertugliflozin and concomitant medications resulting in increased exposure to ertugliflozin are not expected. Similarly, based on published data for other SGLT2 inhibitors with qualitatively similar clearance mechanisms,[12,13,14] increases in ertugliflozin exposure of greater than 2-fold are not expected in subjects with renal or hepatic impairment. Given the well-behaved pharmacokinetic characteristics and the low between-subject variability, the predicted exposure for the 100 mg ertugliflozin dose is expected to adequately cover the extremes of the individual exposures at the therapeutic dose(s) and those that may be observed in patients with renal or hepatic impairment and/or in the presence of interacting concomitant medications.

Reviewer's Comment: The ertugliflozin C_{max} at the supratherapeutic 100 mg ertugliflozin dose (geometric mean of 1735 ng/mL) was ~6.5 times the mean steady-state C_{max} following highest proposed dose of 15 mg qd dose under fasted state (C_{max} of 268.2 ng/mL; Study P035/1051). Amongst the potential worst case scenarios, the subjects with mild, moderate and severe renal impairment had mean increases in AUCinf of ≤1.7-fold, and no clinically meaningful increases in C_{max}. Regarding the interaction with a UGT inhibitor (mefenamic acid), based on PBPK modeling, the predicted ertugliflozin AUC and Cmax ratio (ertugliflozin + mefenamic acid/ertugliflozin alone) were 1.51 and 1.19, respectively. Thus, the choice of supratherapeutic dose appears reasonable for covering any highest clinically relevant exposure scenario due to the effects of intrinsic/extrinsic factors.

4.2.6.3 Instructions with Regard to Meals

All study drugs were administered in the fasted state, after an overnight fast of at least 8 hours.

Reviewer's Comment: Acceptable. Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, but does not alter AUC as compared with the fasted state.

4.2.6.4 ECG and PK Assessments

In each treatment period, the subject was admitted to the PCRU on Day 0. The subject received a single dose of the assigned study medication in the morning of Day 1 in the fasted state.

ECG Assessment: Triplicate 12-lead electrocardiogram (ECG) measurements (approximately 2 to 4 minutes apart) were performed on Days 1 through 3 of each treatment period at : -1, -0.5, 0 hour predose, and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post dose. A semi-automated approach of ECG acquisition/analysis was used. The Investigator who was blinded to the treatment assignments of ertugliflozin and matching placebo performed the review of the ECG data.

PK Assessment: Blood samples were collected following the 0 hour and post-dose ECG measurements at the same time points to evaluate ertugliflozin PK.

Reviewer's Comment: Acceptable. The ECG/PK sampling is adequate to capture effects near T_{max} for the drug (~1-1.5 h) and major metabolites (~2-2.5 h for glucuronide metabolites M5c and M5a) as well as any potential delayed effects up to 48 h post dose.

4.2.7 Baseline

Baseline was defined as the average of the means obtained from the 3 sets of triplicate measurements taken at –1, -0.5 and 0 hours predose on Day 1 within each period.

4.2.8 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.9 Sponsor's Results

4.2.9.1 Study Subjects

Forty-one (41), 40 and 42 subjects received placebo, ertugliflozin and moxifloxacin, respectively. Two (2) subjects were discontinued after receiving moxifloxacin. One subject was discontinued due to increased PR interval prior to dosing in Period 3 after having received placebo and moxifloxacin in Periods 1 and 2, respectively. The other subject was discontinued due to QT prolongation prior to dosing in Period 2 after having received moxifloxacin in Period 1. All 42 treated subjects were included for safety (including ECG data) analyses. All 40 subjects who received ertugliflozin were included in the PK analysis.

Of the 42 subjects who were assigned to study treatment, 20 were male and 22 were female; the majority subjects (32) were white, the mean body weight and BMI were 69.1 kg (range: 51.0 to 95.2 kg) and 23.9 kg/m^2 (range: 19.0 to 27.9 kg/m^2), respectively.

4.2.9.2 Statistical Analyses

4.2.9.2.1 Primary Analysis

The primary endpoint is baseline-adjusted mean difference between ertugliflozin 100 mg and placebo in QTcF. The sponsor used a linear mixed effect model with sequence, period, treatment, time and treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate. The sponsor's concluded that at each of the 10 pre-specified time points post dose, the upper bounds of the 2-sided 90% CIs (equivalent to 1-sided 95% CI) for all the time-matched mean differences between ertugliflozin 100 mg and placebo were less than the pre-defined cutoff of 10 msec (highest value of the upper bound was 4.30 msec). Therefore, a lack of an effect of ertugliflozin on the QTc interval was demonstrated in this study.

Table 2: Sponsor's Statistical Comparisons of QTcF Between Ertugliflozin 100 mg and Placebo at Each Time Point Post Dose by Mixed Effect Model

Nominal Time Hour(s) Post Dose	Least Squares Mean (msec) Test (Ertugliflozin 100 mg)	Least Squares Mean (msec) Reference (Placebo)	Difference (msec) (Test-Reference)	90% Confidence Interval
0.5	414.95	414.85	0.09	(-1.22, 1.40)
1	417.89	415.46	2.43	(1.12, 3.74)
1.5	417.96	416.50	1.47	(0.15, 2.78)
2	416.99	416.68	0.30	(-1.01, 1.62)
3	418.10	415.61	2.49	(1.18, 3.81)
4	418.81	417.31	1.50	(0.19, 2.81)
8	409.15	408.46	0.68	(-0.63, 1.99)
12	411.49	410.97	0.52	(-0.79, 1.83)
24	413.36	410.37	2.99	(1.68, 4.30)
48	410.15	409.33	0.81	(-0.50, 2.12)

Mixed effect model with sequence, period, treatment, time and treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate, was used.
Abbreviations: msec = milliseconds; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Mixed effect model with sequence, period, treatment, time and treatment-by-time interaction as fixed effects, subject within sequence as a random effect and baseline QTcF as a covariate, was used.
Abbreviations: msec = milliseconds; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our ΔΔQTcF results are similar as those reported by the sponsor.

4.2.9.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcF effect for moxifloxacin. Assay sensitivity was confirmed by the moxifloxacin that the lower bounds of the 90% CI above 5 ms at all predefined time points (2, 3, and 4 hours: 10.9 ms, 13.3 ms, and 11.8 ms). The lower bound of the 2- sided 90% CI for the mean difference between moxifloxacin and placebo was greater than 5 ms, therefore, the assay sensitivity was established.

Table 3: Sponsor's Statistical Comparisons of QTcF Between Moxifloxacin 400 mg and Placebo at Each Time Point Post Dose by Mixed Effect Model

Nominal Time Hours Post Dose	Least Squares Mean (msec)		Difference (msec) (Test-Reference)	90% CI	Adjusted 1-sided P-value
	Test (Moxifloxacin 400 mg)	Reference (Placebo)			
2	430.19	417.31	12.87	(10.90, 14.85)	<0.0001
3	431.24	416.24	15.00	(13.03, 16.98)	<0.0001
4	431.73	417.94	13.79	(11.81, 15.76)	<0.0001

Mixed effect model with sequence, period, treatment, time and treatment-by-time interaction as fixed effects and subject within sequence as a random effect and baseline QTcF as a covariate, was used.
The 1-sided p-value of the mean difference between moxifloxacin and placebo in QTcF compared to 5 msec at each pre-specified time point (2, 3, or 4 hours) post dose were computed.
Abbreviations: CI = confidence interval; msec = milliseconds; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our results are similar to the sponsor's QTcF effect for moxifloxacin.

4.2.9.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject had QTc > 480 ms and no subject had ΔQTcF > 60 ms.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our results are similar to the sponsor's QTcF effect for moxifloxacin.

4.2.9.3 Safety Analysis

There were no deaths, SAEs, severe AEs, discontinuations or dose reductions due to AEs reported in the study. There were no ECI (overdose or elevated liver enzymes) reported in the study. A summary of all-causality (treatment-related) treatment-emergent AEs (TEAEs) is provided in Table 4. Overall, 8 subjects experienced 10 AEs after receiving ertugliflozin 100 mg, 18 subjects experienced 20 AEs after receiving moxifloxacin 400 mg and 16 subjects experienced 17 AEs after receiving placebo, the majority of the AEs were considered treatment-related, and were mild in severity.

Table 4: Sponsor's Overview of All-Causality (Treatment-Related) Treatment-Emergent Adverse Events

Number of Subjects	Placebo	Ertugliflozin 100 mg	Moxifloxacin 400 mg
Subjects evaluable for AEs	41	40	42
Number of AEs	17 (14)	10 (9)	20 (16)
Number of subjects with			
AEs	16 (13)	8 (7)	18 (16)
SAEs	0	0	0
Severe AEs	0	0	0
Discontinuation due to AEs	0	0	0
Dose reduced or temporary discontinuation due to AEs	0	0	0

Except for the number of AEs, subjects were counted only once per treatment in each row. Included all data collected since the first dose of study drug. Abbreviations: AE = adverse event; SAE = serious AE.

4.2.9.4 Clinical Pharmacology

4.2.9.4.1 Pharmacokinetic Analysis

The PK results of ertugliflozin are presented in Table 5 and demonstrated in Figure 1. Following a single ertugliflozin 100 mg oral dose, ertugliflozin was rapidly absorbed with a median Tmax of 1.5 hours. Geometric mean Cmax and AUCinf were 1735 ng/mL and 10,290 ng•hr/mL, respectively. The observed geometric mean Cmax value was within 10% of that predicted for ertugliflozin 100 mg single dose administered as tablets under fasted conditions (1600 ng/mL) based on data derived from Study B1521001 assuming linear kinetics and similar bioavailability between solution/suspension and tablet formulations. Variability in ertugliflozin exposure based on geometric %CV was 32% for Cmax and 25% for AUCinf.

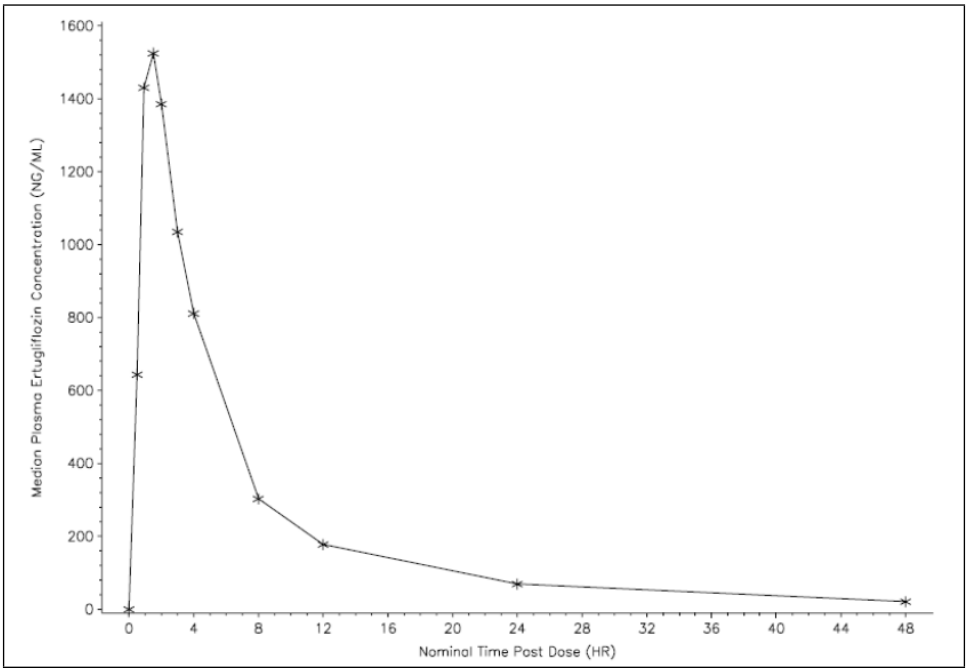
Table 5: **Summary of Plasma Ertugliflozin Pharmacokinetic Parameter Values**

Parameter (unit)	Parameter Summary Statistics[a]
N, n	40, 40
AUC_{inf} (ng•hr/mL)	10290 (25)
AUC_{last} (ng•hr/mL)	9932 (24)
C_{max} (ng/mL)	1735 (32)
T_{max} (hr)	1.50 (0.517, 3.00)
$t_{½}$ (hr)	11.55 ± 2.47

Source: Table 14.4.3.1.1
Pharmacokinetic parameters are defined in Table 3.
Abbreviations: %CV = percent coefficient of variation; N = number of subjects in the treatment group; n = number of subjects with reportable $t_{½}$ and AUC_{inf}; SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.

Source: Table 11 on page 48 of Applicant's CSR p010v01

Figure 1: **Median Plasma Ertugliflozin Concentration-Time Profile Following a Single Oral 100 mg Dose**



Source: Adapted from Figure 1 on page 47 of Applicant's CSR p010v01

4.2.9.4.2 Exposure-Response Analysis

No exposure-response analysis was conducted by the Applicant in this study report.

Reviewer's Analysis: We provided our independent analysis in Section 5.3. A plot of ΔΔQTcF vs. ertugliflozin concentrations is presented in Figure 4.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

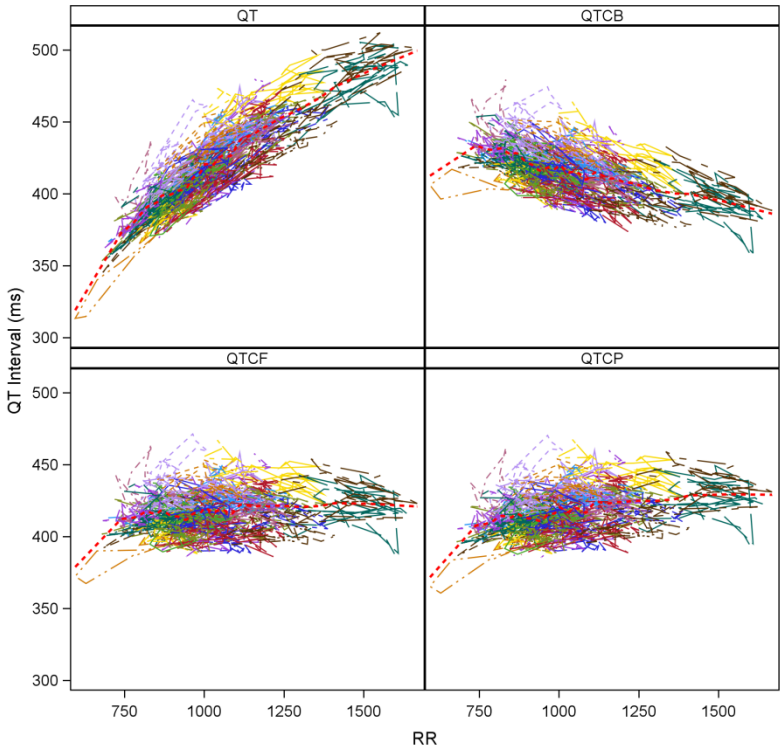
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF is better than QTcP and QTcB. To be consistent with the sponsor's analyses, this reviewer used QTcF in the primary statistical analysis. We performed a secondary analysis using QTcP and obtained similar results.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcP	
	N	MSSS	N	MSSS	N	MSSS
Ertugliflozin 100 mg	40	0.0042	40	0.0021	40	0.0031
Moxifloxacin 400 mg	42	0.0053	42	0.0039	42	0.0050
Placebo	41	0.0037	41	0.0018	41	0.0028
All	42	0.0043	42	0.0028	42	0.0038

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Ertugliflozin

The statistical reviewer used mixed model to analyze the ΔQTcF **and ΔΔQTcF**. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 7 for QTcF. The largest upper bounds of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo is 5.5 ms. The results of QTcF and QTcP (see Table 8) are similar that the upper bounds of the treatment groups are lower than 10 ms of the regulatory concern as described in ICH E14 guidelines.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Ertugliflozin 100 mg and 400 mg Moxifloxacin

		Treatment Group						
	Placebo	Ertugliflozin 100 mg N=40			Moxifloxacin 400 mg N=42			
	ΔQTcF	ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF		
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	Adj* 90% CI
0.5	-1.3	-1.1	0.2	(-2.0, 2.4)	6.4	7.7	(5.5, 9.9)	(4.7, 10.7)
1	-0.7	1.8	2.5	(0.2, 4.8)	11.9	12.6	(10.3, 14.9)	(9.5, 15.7)
1.5	0.3	1.9	1.6	(-0.5, 3.7)	12.4	12.1	(10.1, 14.2)	(9.3, 14.9)
2	0.5	0.9	0.4	(-1.6, 2.4)	13.2	12.7	(10.8, 14.7)	(10.1, 15.4)
3	-0.5	2.0	2.5	(0.0, 5.1)	14.3	14.9	(12.4, 17.4)	(11.5, 18.3)
4	1.1	2.7	1.6	(-0.9, 4.1)	14.8	13.7	(11.2, 16.1)	(10.3, 17.1)
8	-7.7	-7.0	0.7	(-2.1, 3.4)	3.7	11.4	(8.7, 14.1)	(7.7, 15.1)
12	-5.2	-4.6	0.5	(-2.1, 3.2)	3.8	8.9	(6.3, 11.6)	(5.3, 12.5)
24	-5.8	-2.8	3.0	(0.5, 5.5)	1.8	7.6	(5.1, 10.0)	(4.2, 11.0)
48	-6.8	-6.0	0.8	(-2.4, 3.9)	-6.7	0.1	(-3.0, 3.2)	(-4.2, 4.4)

Table 8: Analysis Results of ΔQTcP and ΔΔQTcP for Ertugliflozin 100 mg and 400 mg Moxifloxacin

		Treatment Group					
		Ertugliflozin 100 mg			Moxifloxacin 400 mg		
	ΔQTcP	ΔQTcP	ΔΔQTcP		ΔQTcP	ΔΔQTcP	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0.5	-0.8	-0.9	-0.1	(-2.2, 2.0)	6.4	7.2	(5.1, 9.3)
1	-0.3	2.1	2.4	(0.1, 4.7)	11.4	11.7	(9.4, 14.0)
1.5	0.8	2.4	1.6	(-0.5, 3.6)	12.7	11.9	(9.9, 13.9)
2	0.7	1.2	0.5	(-1.4, 2.4)	13.4	12.7	(10.8, 14.6)
3	-0.2	2.2	2.4	(-0.1, 5.0)	14.5	14.7	(12.2, 17.2)
4	1.3	3.1	1.8	(-0.7, 4.3)	14.8	13.4	(11.0, 15.9)
8	-9.4	-8.3	1.1	(-1.7, 3.9)	2.1	11.5	(8.7, 14.3)
12	-6.5	-5.9	0.5	(-2.2, 3.2)	2.6	9.1	(6.4, 11.8)
24	-6.4	-3.6	2.9	(0.3, 5.4)	1.2	7.6	(5.2, 10.1)
48	-8.1	-7.2	0.9	(-2.2, 4.0)	-8.0	0.1	(-3.0, 3.1)

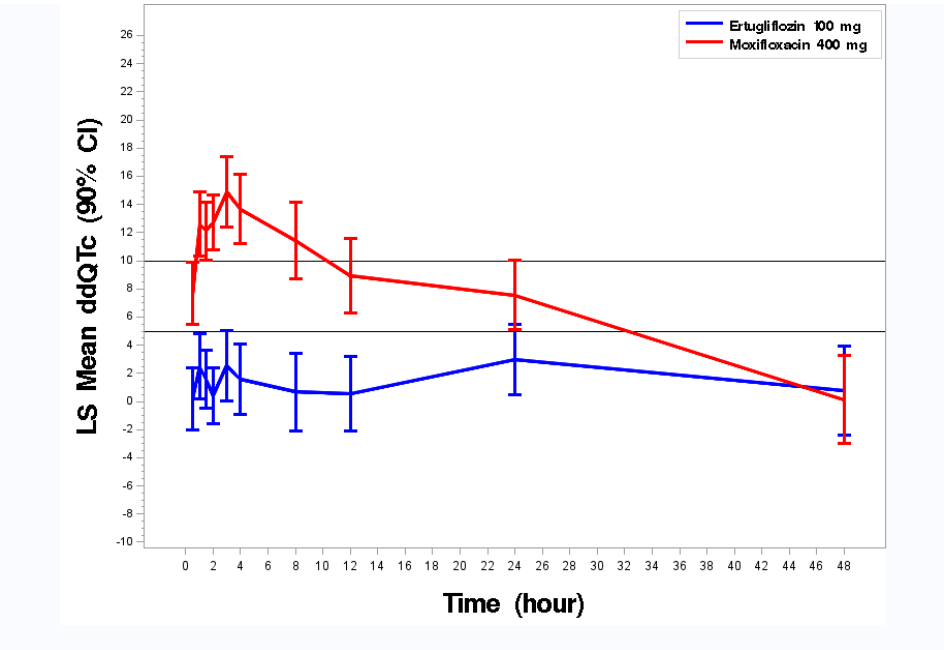
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 12.4 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 11.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays by-time profile of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Time Profile



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, and >500 mg. No subject's QTcF is above 480 ms.

Table 9: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
Ertugliflozin 100 mg	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	42	32 (76.2%)	10 (23.8%)	0 (0.0%)	0 (0.0%)
Placebo	41	40 (97.6%)	1 (2.4%)	0 (0.0%)	0 (0.0%)

Table 10 lists the number of subjects changes from baseline QTc ≤30 ms, between 30 and

60 ms, between 60 ms and 90, and >90 ms. No subject's change from baseline is above 60 ms.

Table 10: **Categorical Analysis of ΔQTcF**

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Ertugliflozin 100 mg	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	42	38 (90.5%)	4 (9.5%)	0 (0.0%)	0 (0.0%)
Placebo	41	41 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effects and baseline as covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo is 2.1 bpm. Table 12 presents the categorical analysis of HR. One subjects who experienced HR interval greater than 100 bpm is in ertugliflozin 100 mg group.

Table 11: Analysis Results of ΔHR and ΔΔHR for Ertugliflozin 100 mg and 400 mg Moxifloxacin

		Treatment Group		
	Placebo	Ertugliflozin 100 mg		
	ΔHR	ΔHR	ΔΔHR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
0.5	-1.6	-0.8	0.8	(-0.4, 1.9)
1	-1.4	-1.2	0.2	(-1.2, 1.5)
1.5	-1.7	-1.6	0.1	(-1.1, 1.4)
2	-0.7	-1.4	-0.8	(-2.1, 0.6)
3	-1.2	-0.6	0.6	(-0.7, 2.0)
4	-0.7	-1.2	-0.5	(-1.8, 0.9)
8	7.5	5.3	-2.2	(-4.1, -0.4)
12	4.9	5.1	0.3	(-1.5, 2.0)
24	2.4	2.8	0.4	(-1.2, 2.1)
48	5.1	4.4	-0.7	(-2.3, 0.9)

Table 12: **Categorical Analysis for HR**

	Total N	HR <= 100 bpm	HR >100 bpm
Ertugliflozin 100 mg	40	39 (97.5%)	1 (2.5%)
Moxifloxacin 400 mg	42	42 (100%)	0 (0.0%)
Placebo	41	41 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effects and baseline as covariate. The analysis results are listed in Table 13. The largest upper bound of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo is 4.6 ms. Table 14 presents the categorical analysis of PR. Two subjects who experienced P R interval greater than 200 ms are in ertugliflozin 100 mg group.

Table 13: Analysis Results of ΔPR and ΔΔPR for Ertugliflozin 100 mg

		Treatment Group		
	Placebo	Ertugliflozin 100 mg		
	ΔPR	ΔPR	ΔΔPR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
0.5	-0.7	-0.2	0.4	(-1.3, 2.2)
1	0.4	-0.4	-0.8	(-2.5, 0.8)
1.5	-0.9	-2.6	-1.7	(-3.5, 0.1)
2	0.1	-0.7	-0.8	(-2.5, 0.8)
3	-0.8	-1.7	-0.9	(-2.9, 1.1)
4	-0.5	-3.1	-2.6	(-4.9, -0.4)
8	-6.6	-6.8	-0.2	(-2.6, 2.1)
12	-5.5	-3.1	2.4	(0.1, 4.6)
24	-0.9	-2.5	-1.7	(-3.7, 0.3)
48	-0.2	1.0	1.1	(-1.0, 3.3)

Table 14: **Categorical Analysis for PR**

	Total N	PR <= 200 ms	PR >200 ms
Ertugliflozin 100 mg	40	38 (95.0%)	2 (5.0%)
Moxifloxacin 400 mg	42	39 (92.9%)	3 (7.1%)
Placebo	41	38 (92.7%)	3 (7.3%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effects and baseline as covariate. The analysis results are listed in Table 15. The largest upper bound of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo is 1.4 ms. Table 16 presents the categorical analysis of QRS. Two subjects who experienced Q R S interval greater than 110 ms are in ertugliflozin 100 mg group.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for Ertugliflozin 100 mg

		Treatment Group		
	Placebo	Ertugliflozin 100 mg		
	ΔQRS	ΔQRS	ΔΔQRS	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
0.5	0.4	0.3	-0.1	(-1.0, 0.8)
1	0.0	0.4	0.4	(-0.7, 1.4)
1.5	-0.0	0.1	0.1	(-0.8, 1.1)
2	-0.2	-0.2	0.1	(-0.7, 0.9)
3	-0.5	0.1	0.6	(-0.1, 1.3)
4	-0.1	-0.6	-0.4	(-1.2, 0.4)
8	-0.5	-1.3	-0.8	(-2.1, 0.5)
12	-0.2	-0.4	-0.2	(-1.5, 1.0)
24	-0.2	-0.6	-0.5	(-1.7, 0.8)
48	-0.7	-0.7	-0.0	(-1.4, 1.3)

Table 16: **Categorical Analysis for QRS**

	Total N	QRS <= 110 ms	QRS > 110 ms
Ertugliflozin 100 mg	40	38 (95.0%)	2 (5.0%)
Moxifloxacin 400 mg	42	40 (95.2%)	2 (4.8%)
Placebo	41	39 (95.1%)	2 (4.9%)

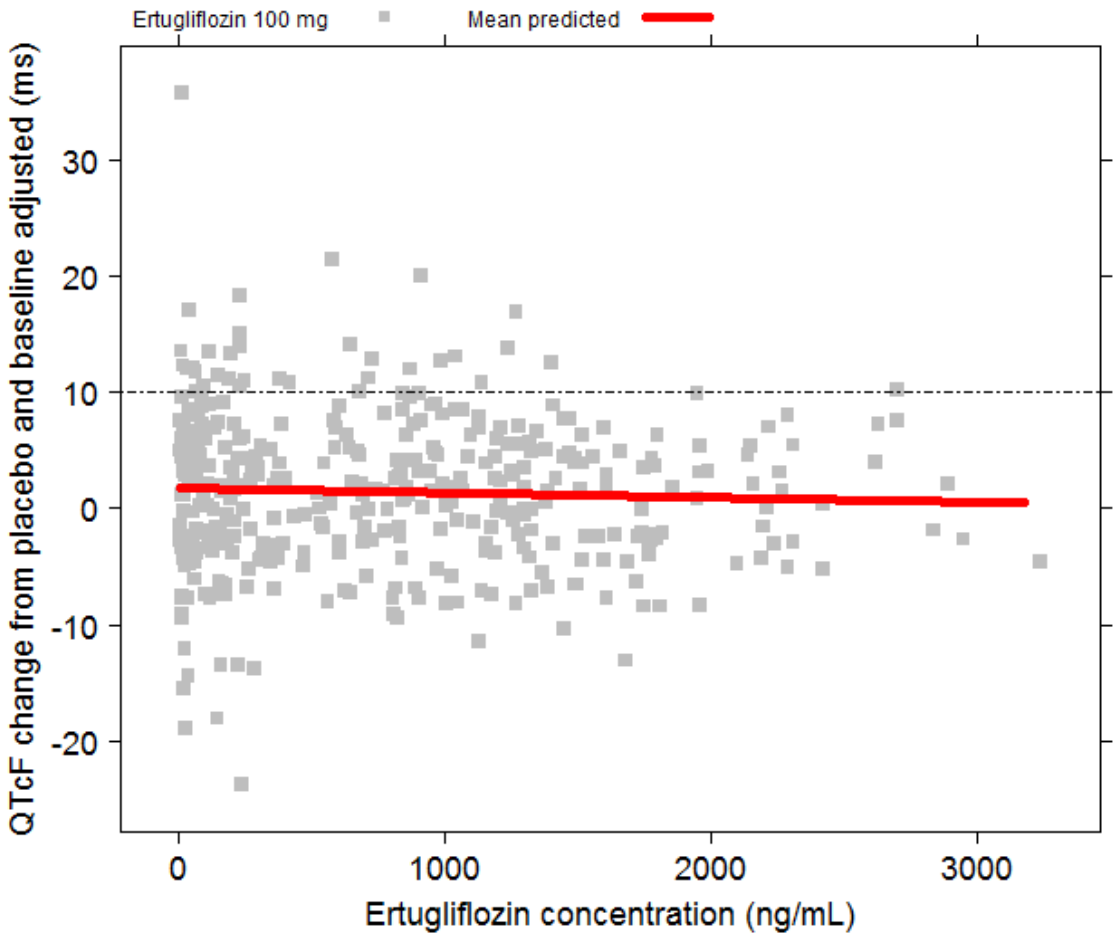
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1 above.

The ertugliflozin C_{max} at the supratherapeutic 100 mg ertugliflozin dose (1735 ng/mL) was ~6.5 times the mean steady-state C_{max} following qd administration at the 15 mg dose in the fasted state (268.2 ng/mL; Study P035/1051), which is the highest proposed therapeutic dose.

The relationship between ΔΔQTcF and ertugliflozin concentrations was investigated by linear mixed-effects modeling. This relationship is visualized in Figure 4, with no evident exposure-response relationship (mean slope estimate of -0.000407 ms per ng/mL, with p-value=0.397).

Figure 4: ΔΔQTcF vs. Ertugliflozin concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure		5 mg once daily or 15 mg once daily, to be taken in the morning, with or without food Geometric mean (%CV) C_{max} and AUC_{inf} after single dose administration of 15 mg were 262.4 ng/mL (21%) and 1354 ng.hr/mL (19%), respectively (Study P023/1037). Geometric mean (%CV) C_{max} and AUC_{tau} at steady state at 15 mg qd were 268.2 ng/mL (20%) and 1193 ng.hr/mL (22%), respectively (Study P035/1051).
Maximum Tolerated Dose		Ertugliflozin was safe and well tolerated at all tested doses. Despite assessing doses as high as 300 mg, a maximum tolerated dose has not been identified. Oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg qd (up to 14 days), and 25 mg qd (up to 12 weeks) were not associated with safety concerns in the Phase 1 (P036/1001 and P037/1002) and Phase 2 (P016/1006) studies.
Principal Adverse Events		Overall, ertugliflozin was safe and well tolerated at both the 5 mg and 15 mg doses across the clinical development program. Information on adverse events can be found in Module 2.7.4 of the ertugliflozin CTD.
Maximum Dose Tested	Single Dose	300 mg (Study P036/1001)
	Multiple Dose	100 mg qd x 14 days (Study P037/1002)
Exposures Achieved at Maximum Tested Dose	Single Dose Geometric Mean (%CV)	Dose: 300 mg (fasted, Study P036/1001) C_{max} = 4330 ng/mL (20%) AUC_{inf} = 26400 ng.hr/mL (16%)
	Multiple Dose Geometric Mean (%CV)	Dose: 100 mg qd x 14 days (light meal, Study P037/1002) C_{max} (Day 14) = 1035 ng/mL (25%) AUC_{tau} (Day 14) = 7761 ng.hr/mL (17%)
Range of Linear PK		Linear and dose-proportional over range of 0.5 to 300 mg single dose, and 1 to 100 mg qd x 14 days.
Accumulation at Steady State		Accumulation ratio 1.1 to 1.4 after once daily dosing (Studies P037/1002, P041/1009)

Metabolites		Glucuronidation is the major metabolic pathway (86%) for ertugliflozin, with minor contributions from oxidative metabolism (12%). The 3-O-β glucuronide (M5c or PF-06481944) and 2-O-β glucuronide (M5a or PF-06685948) are considered the primary circulating metabolites of ertugliflozin. The IC_{50} values of M5c and M5a for SGLT2 inhibition were >1000 nM and 476 nM, respectively, compared to 0.877 nM for ertugliflozin. Therefore, both metabolites are >500-fold less potent than ertugliflozin for SGLT2 inhibition and are pharmacologically inactive at clinically relevant concentrations.
Absorption	Absolute Bioavailability GMR (90% CI)	104.73% (101.64%-107.91%) [Study P020/1043]
	T_{max} Median (range)	Ertugliflozin: 1.0 (1.0 - 3.0) hours [fasted state, commercial tablet, Study P024/1048] Ertugliflozin: 2.0 (1.0 - 6.0) hours [fed state, commercial tablet, Study P024/1048] M5c: 2.00 (1.00-3.00) hours [fasted state, healthy subjects, Study P014/1024] M5a: 2.50 (2.00-4.00) hours [fasted state, healthy subjects, Study P014/1024]
Distribution	Vss Geometric mean (%CV)	85.5 L (15%) [Study P020/1043]
	% bound	93.6%
Elimination	Route	In the ADME study (P038/1003), excretion of radioactivity in urine and feces accounted for 50.2% and 40.9% of the dose, respectively. Primary clearance mechanism is metabolism via glucuronidation (UGT1A9 and UGT2B7). Renal excretion of unchanged ertugliflozin accounted for 1.5% of the administered dose.
	Half-life	Based on the population PK analysis, the mean elimination half-life (%CV) was estimated to be 15.3 hours (7.89%) for healthy subjects and 16.6 hours (15.5%) for T2DM patients with normal renal function. Mean (SD) half-life values for metabolites M5c and M5a

		are as follows: M5c: 14.99 (6.10) hours [healthy subjects, Study P014/1024] M5a: 13.43 (5.16) hours [healthy subjects, Study P014/1024]
	CL Geometric mean (%CV)	187.2 mL/min (15%) [Study P020/1043]
Intrinsic Factors	T2DM patients	Ertugliflozin PK were similar in T2DM patients and healthy subjects [Study P009/1023]. Based on the population PK analysis, T2DM patients had an ~11% increase in AUC_{tau} compared to healthy subjects which is not considered clinically relevant.
	Age	No effect of age on PK based on the population PK analysis.
	Sex	Based on the population PK analysis, females had a 4% increase in AUC_{tau} compared to males. Females also had a 36% higher Vc/F compared to males, which would be expected to decrease C_{max}. The changes in AUC_{tau} and C_{max} are not considered clinically relevant
	Race	Based on the population PK analysis, Asian subjects had a 7% decrease in AUC_{tau} compared to white subjects. Asians also had a 112% higher Vc/F compared to white subjects, which would be expected to decrease C_{max}. The changes in AUC_{tau} and C_{max} are not considered clinically relevant. Black subjects and subjects of other race did not have a meaningful effect on PK.
	Hepatic & Renal Impairment	Hepatic impairment: In subjects with moderate hepatic impairment (Study P014/1024), ertugliflozin AUC_{inf} and C_{max} decreased by approximately 13% and 21%, respectively, compared to the normal hepatic function group. The decrease in exposure is not considered clinically meaningful. Ertugliflozin PK have not been evaluated in subjects with severe hepatic impairment. Renal Impairment: In the renal impairment study (Study P009/1023), the predicted mean AUC_{inf} values for mild, moderate and severe renal impairment were ≤70% (≤1.7-fold) higher relative to subjects with normal renal function. There were no clinically meaningful differences in the geometric mean C_{max} values among

		the different renal function groups.
Extrinsic Factors	Drug Interactions	Single dose administration of sitagliptin 100 mg, metformin 1000 mg, glimepiride 1 mg or simvastatin 40 mg had no meaningful effect on the PK of ertugliflozin 15 mg (90% CIs for the GMR of AUC and C_{max} were within equivalence limits of 80.00%-125.00%). Single dose administration of 15 mg ertugliflozin did not have a clinically meaningful effect on the PK of sitagliptin 100 mg, metformin 1000 mg, glimepiride 1 mg or simvastatin 40 mg. Rifampin (UGT and CYP inducer): The GMRs and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for co-administration with rifampin 600 mg qd x 10 days vs ertugliflozin alone were 61.16% (90% CI: 57.22%-65.37%) and 84.62% (90% CI: 74.17%-96.53%), respectively. No dose adjustment is needed when co-administered with rifampin. Mefenamic acid (UGT inhibitor): Based on PBPK modeling, the predicted ertugliflozin AUC and C_{max} ratio (ertugliflozin + mefenamic acid/ertugliflozin alone) were 1.51 [95% CI: 1.48-1.54] and 1.19 (95% CI: 1.17-1.20), respectively. The change in ertugliflozin exposure is not considered clinically meaningful.
	Food Effect	Following administration of a 15 mg commercial tablet with a high-fat, high-calorie breakfast (Study P024/1048), the 90% CI for ertugliflozin AUC_{inf} GMR was within the acceptance range for BE (80% to 125%), indicating no clinically meaningful differences in the overall exposure in the fed vs fasted states. Food decreased C_{max} by 29% and increased T_{max} from 1 hour (fasted) to 2 hours (fed).
Expected High Clinical Exposure Scenario		Based on the information summarized above, clinical scenarios where ertugliflozin exposure is increased by more than 1.7-fold are not anticipated. In the thorough QT study (P010/1025), the ertugliflozin C_{max} at the supratherapeutic 100 mg ertugliflozin dose [geometric mean (%CV) 1735 ng/mL (32%)] was ~6.5 times the mean steady-state C_{max} following qd administration at the 15 mg dose in the fasted state (C_{max} of 268.2 ng/mL; Study P035/1051) and adequately

	covers the extremes of the individual exposures at the proposed therapeutic dose(s) and those that may be observed in patients with renal or hepatic impairment and/or in the presence of interacting concomitant medications.
Preclinical Cardiac Safety	Cardiovascular safety of ertugliflozin was assessed in vitro and in vivo. At concentrations of 19, 38 and 114 μM, ertugliflozin produced 29.1%, 45.5%, and 60.3% inhibition of hERG current amplitude, respectively, with a calculated IC_{50} of 59 μM and IC_{20} of 8.1 μM. An IC_{50} of 59 μM (25.19 μg/mL) is approximately 1465x the human unbound drug steady state C_{max} (0.0172 μg/mL) at a dose of 15 mg/day. In the in vivo cardiovascular study, dogs were administered 1, 5, and 50 mg/kg in a cross-over design. During the 24-hour postdose observation period, there were no ertugliflozin-related effects on any hemodynamic, electrocardiographic, myocardial contractility, or activity parameters at 1 and 5 mg/kg. At 50 mg/kg, there was a 6 msec decrease in corrected QT interval and a decrease of 489 mmHg/sec in left ventricular contractility, with a concomitant increase of 4 msec in PR interval near T_{max} (3.5 hours). An increase of 6 mmHg in systolic blood pressure and a decrease of 6 beats/min in heart rate commenced 8 hours postdose. All parameters returned to control values after 24 hours. At the no observed effect level of 5 mg/kg, the unbound plasma ertugliflozin concentration at 7 hours postdose was 0.062 μg/mL, approximately 4x greater than the human unbound steady state C_{max} of 0.0172 μg/mL at 15 mg/day. Therefore, cardiovascular effects are unlikely at the human efficacious exposure.
Clinical Cardiac Safety	The Phase 3 development program included 4,859 subjects who were randomized and treated in 7 Phase 3 studies. Among these subjects, 1716 were randomized to ertugliflozin 5 mg daily and 1693 were randomized to ertugliflozin 15 mg daily. There was no meaningful difference in the proportion of ertugliflozin-treated subjects meeting thresholds of clinical concern for QTcF relative to the non-ertugliflozin treated subjects. Similarly, there were no clinically meaningful differences in the mean change in ECG parameters (heart rate, PR, QRS, QT, QTcB, and QTcF interval) across the ertugliflozin 5 mg and 15 mg groups and placebo groups in a pool of 3 placebo-controlled studies

	(N=1544). The proportion of subjects with a specific adverse event potentially related to an effect on QT (QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths) was low (≤0.5%) in all groups. In addition, a Cardiovascular Adjudication Committee adjudicated, in a blinded fashion, potential cases of CV events, venous thromboembolic events, hospitalization for heart failure, and all deaths in all Phase 3 studies. The Program DMC reviewed the results of the CV meta-analysis and reported that the upper bound of the adjusted 95% confidence interval for the hazard ratio for major adverse cardiac events plus was <1.8, ruling out an 80% increase in CV risk relative to the non-ertugliflozin comparator group, and meeting the United States Food and Drug Administration requirements for submission of a diabetes drug NDA. In a Phase 1 thorough QT study (P010/1025), a lack of an effect on QTc interval was demonstrated with a single supratherapeutic oral dose of ertugliflozin 100 mg. Additionally, there were no clinically significant changes in ECG parameters after administration of ertugliflozin 100 mg in this study.

Abbreviations: %CV=percent coefficient of variation; ADME=absorption, distribution, metabolism, excretion; AUC=area under the plasma concentration-time curve; AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; AUC_{tau}=area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where tau=24 hours; CI=confidence interval; C_{max}=maximum observed plasma concentration; CTD=Common Technical Document; CV=cardiovascular; CYP=cytochrome P450; DDI=drug-drug interactions; DMC=data monitoring committee; ECG=electrocardiogram; GMR=geometric mean ratio; IC_{50}= half maximal inhibitory concentration; NDA=New Drug Application; PBPK= physiologically based PK modeling; PK=pharmacokinetics; qd=once-daily; SD=standard deviation; SGLT2= sodium-glucose co-transporter 2; T2DM=type 2 diabetes mellitus; T_{max}= time to first occurrence of C_{max}; UGT= uridine diphosphate-glucuronosyltransferase

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/s/

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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:	May 4, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209803
Product Name and Strength:	Steglatro (ertugliflozin) tablets 5 mg, and 15 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	December 19, 2016 and April 13, 2017
OSE RCM #:	2016-2925
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed label and labeling for Steglatro (ertugliflozin) NDA 209803 for areas of vulnerability that could lead to medication errors. The Division of Metabolism and Endocrinology Products (DMEP) has requested this review as part of their evaluation to the 505(b)(1) NDA submission for Steglatro on December 19, 2016.

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
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck Sharp and Dohme Corp. submitted NDA 209803 Steglatro (ertugliflozin) as a 505(b)(1) for use an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. We performed a risk assessment of the proposed container label, carton label, and prescribing information (PI) to identify deficiencies that may lead to medication errors and other areas of improvement.

We identified areas of the proposed labeling that could be improved to promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the container label and carton labeling to address these deficiencies.

For the Division, we provide a recommendation to include the temperature unit in the storage information section. For the Applicant we provide recommendations for the carton/container regarding the tablet image, temperature unit inclusion, format of expiration date, and location of NDC number on blister packaging.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. **PRESCRIBING INFORMATION (PI)**

1. **Section 16: How Supplied/Storage and Handling**
   Revise the currently partial storage temperature range to include the "C" for Centigrade and "F" for Fahrenheit to both specified temperature ranges. For example, revise the current "20-25°C (68-77°F)" to "20°C-25°C (68°F-77°F)", since the updated format will eliminate possible confusion in the interpretation of the storage temperature.

4.2 RECOMMENDATIONS FOR MERCK SHARP AND DOHME CORP.

We recommend the following be implemented prior to approval of this NDA 209803:

A. Trade and Hospital Unit Dose Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4) -shaped rather than the proposed triangular-shape. In addition, the featured color for the tablets is (b) (4) rather than the proposed pink for 5 mg tablet, and red for 15 mg tablet as stated in the PI. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.[a]
2. Replace "Trademark" with conditionally acceptable Proprietary Name, Steglatro, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the Carton Labeling. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry[a], where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet].FDA. April 2013 [cited 2017 April 13]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

1. We note your intention to include a 30 count sample of the 5 mg and 15 mg tablet. Please include the carton labeling for the 30 count 5 mg and 15 mg tablet.
2. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(i).
3. Please include the expiration date on sample carton labeling if possible.
4. Please include the NDC on sample carton labeling if possible.
5. Please increase the font size of the statement "Sample Not for Sale" as currently presented it is small making it difficult to read.
6. See. A.4.

D. Trade and Sample Container Labels

1. See A.1. through A.4.

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April, 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Steglatro (ertugliflozin) that Merck Sharp and Dohme submitted on December 19, 2016.

Table 2. Relevant Product Information for Steglatro (ertugliflozin)	
Initial Approval Date	N/A
Active Ingredient	Ertugliflozin
Indication	Treatment of patients with Type 2 Diabetes Mellitus
Route of Administration	Oral
Dosage Form	Tablets
Strength	5 mg, 15 mg
Dose and Frequency	Dose and Frequency: Recommended starting dose is 5 mg once daily in the morning with or without food. In patients tolerating 5 mg who require additional glycemic control, the dose may be increased to 15 mg once daily.
How Supplied	Steglatro tablets, 5 mg, are pink, triangular-shaped, biconvex, film-coated tablets with "701" debossed on one side and plain on the other side. They are supplied as follows: NDC 0006-5363-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5363-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5363-03 unit-of-use bottles of 30 NDC 0006-5363-06 unit-of-use bottles of 90 NDC 0006-5363-07 bulk bottles of 500 Steglatro tablets, 15 mg, are red, triangular-shaped, biconvex, film-coated tablets with "702" debossed on one side and plain on the other side. They are supplied as follows: NDC 0006-5364-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5364-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5364-03 unit-of-use bottles of 30 NDC 0006-5364-06 unit-of-use bottles of 90 NDC 0006-5364-07 bulk bottles of 500
Storage	**Storage of Bottles**

	Store at 20°C - 25°C (68°F - 77°F), excursions permitted between 15°C - 30°C (59°F to 86°F). Protect from moisture. Store in a dry place. **Storage of Blisters** Store at 20°C - 25°C (68°F - 77°F), excursions permitted between 15°C - 30°C (59°F to 86°F). Store in the original package.
Container Closure	The intended trade package configuration consists of high-density polyethylene (HDPE) bottles with (b) (4) closures for potential total product counts of weekly, 30-day and 90-day supply and pharmacy re-dispensing bottles of 500s with non CR closures. The intended sample package configuration will be a weekly HDPE bottle. The intended hospital unit dose (HUD) package is unit-of-use foil/foil blister packages of 30 (5 blister cards of 6 tablets)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 5, 2017, we searched the L:drive and AIMS using the terms, Steglatro to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous Proprietary Name Reviews [b,c].

[b] Conrad, A. Proprietary Name Review for Steglatro (IND 106447). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 April 6. Panorama No. 2016-2484877.

[c] Ogbonna, C. Proprietary Name Review for Steglatro (NDA 209803). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 March 22. Panorama No. 2017-12352707.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Steglatro (ertugliflozin) labels and labeling submitted by Merck Sharp & Dohme Corp. on December 19, 2016.

- Container label
- Carton labeling
- Professional Sample Blister cards
- Professional Sample Carton Labeling
- Hospital Unit-Dose Blister labels
- Medication Guide
  \\cdsesub1\evsprod\nda209803\0000\m1\us\01-crt-usmg-mk8835-t-original.doc
- Prescribing Information
  \\cdsesub1\evsprod\nda209803\0000\m1\us\01-crt-uspi-mk8835-t-original.doc

G.2 Label and Labeling Images

Container Labels:

(b) (4)

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

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

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

/s/

CASMIR I OGBONNA
05/04/2017

HINA S MEHTA
05/04/2017

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:	May 4, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209805
Product Name and Strength:	Steglujan (ertugliflozin/sitagliptin) oral tablet Ertugliflozin 5 mg/sitagliptin 100 mg Ertugliflozin 15 mg/sitagliptin 100 mg (b) (4)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	December 19, 2016
OSE RCM #:	2016-2928
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed label and labeling for Steglujan (ertugliflozin/sitagliptin) NDA 209805 for areas of vulnerability that could lead to medication errors. The Division of Metabolism and Endocrinology Products (DMEP) has requested this review as part of their evaluation to the 505(b)(1) NDA submission for Steglujan on December 19, 2016.

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
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck Sharp and Dohme Corp. submitted NDA 209805 Steglujan as a 505(b)(1) for use an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. We performed a risk assessment of the proposed container label, carton label, and prescribing information (PI) to identify deficiencies that may lead to medication errors and other areas of improvement.

We identified areas of the proposed labeling that could be improved to promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the container label and carton labeling to address these deficiencies.

For the Division, we provide a recommendation to include the temperature unit in the storage information section. For the Applicant we provide recommendations for the carton/container regarding the tablet, image temperature unit inclusion, format of expiration date, and location of NDC number on blister packaging.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. PRESCRIBING INFORMATION (PI)

1. **Section 16: How Supplied/Storage and Handling**
   Revise the currently partial storage temperature range to include the "C" for Centigrade and "F" for Fahrenheit to both specified temperature ranges. For example, revise the current "20-25°C (68-77°F)" to "20°C-25°C (68°F-77°F)", since the updated format will eliminate possible confusion in the interpretation of the storage temperature.

4.2 RECOMMENDATIONS FOR MERCK SHARP AND DOHME CORP.

We recommend the following be implemented prior to approval of this NDA 209805:

A. Trade and Hospital Unit Dose Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4)-shaped rather than the proposed almond-shape. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.[a]
2. Replace the word "Trademark" with conditionally acceptable Proprietary Name, Steglujan, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the HUD and Trade Carton Labels. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry[a], where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

1. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(i).
2. Please include the expiration date on sample carton labeling if possible.
3. Please include the NDC on sample carton labeling if possible.
4. Please increase the font size of the statement “Sample Not for Sale” as currently presented it is small making it difficult to read.
5. See. A.4.

D. Trade and Sample Container Labels

1. See A.1 through A.4.

[a] FDA-CDER Draft Guidance for Industry. Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. April, 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Steglujan (ertugliflozin/sitagliptin) that Merck Sharp and Dohme submitted on December 19, 2016.

Table 2. Relevant Product Information for Steglujan (ertugliflozin/sitagliptin)	
Initial Approval Date	N/A
Active Ingredient	Ertugliflozin and Sitagliptin
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate
Route of Administration	Oral
Dosage Form	Tablet
Strength	Ertugliflozin 5 mg/sitagliptin 100 mg Ertugliflozin 15 mg/sitagliptin 100 mg (b) (4)
Dose and Frequency	The recommended starting dose of Steglujan is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating Steglujan, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin, once daily, if additional glycemic control is needed. For patients treated with ertugliflozin who are being switched to Steglujan, the dose of ertugliflozin can be maintained. In patients with volume depletion, correcting this condition prior to initiation of Steglujan is recommended. **Patients with Renal Impairment** Assessment of renal function is recommended prior to initiation of Steglujan and periodically thereafter. Initiation of Steglujan is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than (b) (4)

	(b) (4) [redacted]
How Supplied	(b) (4) [redacted] Steglujan tablets, 5 mg/100 mg, are beige, almond-shaped, film-coated tablets debossed with “554” on one side and plain on the other side. They are supplied as follows: NDC 0006-5367-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5367-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5367-03 unit-of-use bottles of 30 NDC 0006-5367-06 unit-of-use bottles of 90 NDC 0006-5367-07 bulk bottles of 500

	Steglujan tablets, 15 mg/100 mg, are brown, almond-shaped, film-coated tablets debossed with “555” on one side and plain on the other side. They are supplied as follows: NDC 0006-5368-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5368-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5368-03 unit-of-use bottles of 30 NDC 0006-5368-06 unit-of-use bottles of 90 NDC 0006-5368-07 bulk bottles of 500
Storage	**Storage of Bottles** Store at 20°C - 25°C (68°F - 77°F), excursions permitted between 15°C - 30°C (59°F to 86°F). Protect from moisture. Store in a dry place. **Storage of Blisters** Store at 20°C - 25°C (68°F - 77°F), excursions permitted between 15°C - 30°C (59°F to 86°F). Store in the original package.
Container Closure	The intended trade package configuration consists of high-density polyethylene (HDPE) bottles with (b) (4) closures for potential total product counts of weekly, 30-day and 90-day supply and pharmacy re-dispensing bottles of 500s with non CR closures. The intended sample package configuration will be a weekly HDPE bottle. The intended hospital unit dose (HUD) package is unit-of-use foil/foil blister packages of 30 (5 blister cards of 6 tablets)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 6, 2017, we searched the L:drive and AIMS using the terms, Steglujan to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous reviews[b], and we confirmed that our previous recommendations were implemented or considered.

[b] Rychlik, I. Proprietary Name Review for Steglujan IND 122330. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 06. RCM No. 2016-9221329

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis[c], along with postmarket medication error data, we reviewed the following Steglujan labels and labeling submitted by Merck Sharp and Dohme on December 19, 2016.

- Container label
- Carton labeling
- Professional Sample Blistercards
- Professional Sample Carton Labeling
- Hospital Unit-Dose Blister labels
- Medication Guide
  \\cdsesub1\evsprod\nda209805\0000\m1\us\01-crt-usmg-mk8835a-t-original.doc
- Prescribing Information (PI)
  \\cdsesub1\evsprod\nda209805\0000\m1\us\01-crt-uspi-mk8835a-t-original.doc

G.2 Label and Labeling Images

Container Labels:

(b) (4)

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

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

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/s/

CASMIR I OGBONNA
05/04/2017

HINA S MEHTA
05/04/2017

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:	May 4, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209806
Product Name and Strength:	Segluromet (ertugliflozin/metformin) oral tablet Ertugliflozin 2.5 mg / Metformin 500 mg Ertugliflozin 2.5 mg / Metformin 1000 mg Ertugliflozin 7.5 mg / Metformin 500 mg Ertugliflozin 7.5 mg / Metformin 1000 mg
Product Type:	Multi-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp and Dohme Corp.
Submission Date:	December 19, 2016
OSE RCM #:	2016-2931
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP.
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed label and labeling for Segluromet (ertugliflozin/metformin) NDA 209806 for areas of vulnerability that could lead to medication errors. The Division of Metabolism and Endocrinology Products (DMEP) has requested this review as part of their evaluation to the 505(b)(2) NDA submission for Segluromet on December 19, 2016.

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
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck Sharp and Dohme Corp. submitted NDA 209806 Segluromet as a 505(b)(2) for use an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. We performed a risk assessment of the proposed container label, carton label, and prescribing information (PI) to identify deficiencies that may lead to medication errors and other areas of improvement.

We identified areas of the proposed labeling that could be improved to promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the container label and carton labeling to address these deficiencies.

For the Division, we provide a recommendation to include the temperature unit in the storage information section. For the Applicant we provide recommendations for the carton/container regarding the tablet, image temperature unit inclusion, format of expiration date, and location of NDC number on blister packaging.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. PRESCRIBING INFORMATION (PI)

1. **Section 16: How Supplied/Storage and Handling**
   Revise the currently partial storage temperature range to include the "C" for Centigrade and "F" for Fahrenheit to both specified temperature ranges. For example, revise the current 20-25°C (68-77°F) to 20°C-25°C (68°F-77°F), since the updated format will eliminate possible confusion in the interpretation of the storage temperature.

4.2 RECOMMENDATIONS FOR MERCK SHARP AND DOHME CORP.

We recommend the following be implemented prior to approval of this NDA 209806:

A. Trade and Hospital Unit Dose (HUD) Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4)-shaped rather than the proposed oval-shape. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.[a]
2. Replace the word "Trademark" with conditionally acceptable Proprietary Name, Steglatro, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the HUD and Trade Carton Labels. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry[a], where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

a. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(i).
b. Please include the expiration date on sample carton labeling if possible.
c. Please include the NDC on sample carton labeling if possible.
d. Please increase the font size of the statement "Sample Not for Sale" as currently presented it is small making it difficult to read.
e. See A.4.

D. Trade and Sample Container Labels

1. See A.1 through A.4.

[a] FDA-CDER Draft Guidance for Industry. Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. April, 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Segluromet (ertugliflozin/metformin) that Merck Sharp and Dohme Corp. submitted on December 19, 2016.

Table 2. Relevant Product Information for Segluromet (ertugliflozin/metformin)	
Initial Approval Date	N/A
Active Ingredient	Ertugliflozin and Metformin
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
Route of Administration	Oral
Dosage Form	Tablet
Strength	Ertugliflozin 2.5 mg / Metformin 500 mg Ertugliflozin 2.5 mg / Metformin 1000 mg Ertugliflozin 7.5 mg / Metformin 500 mg Ertugliflozin 7.5 mg / Metformin 1000 mg
Dose and Frequency	Individualize the starting dose of Segluromet (ertugliflozin and metformin hydrochloride) based on the patient's current regimen: • In patients on metformin, switch to Segluromet tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin. • In patients on ertugliflozin, switch to Segluromet tablets containing 500 mg metformin, with a similar total daily dose of ertugliflozin. • In patients already treated with ertugliflozin and metformin, switch to Segluromet tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin. Take Segluromet twice daily with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin. • In patients with volume depletion not previously treated with ertugliflozin, correcting this condition prior to initiation of Segluromet is recommended. • Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and

	2,000 mg metformin HCl. **PATIENTS WITH RENAL IMPAIRMENT** Assess renal function prior to initiation of Segluromet and periodically thereafter. • Segluromet is contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 • Initiation of Segluromet is not recommended in patients with an eGFR (b) (4) • (b) (4) • Use of Segluromet is not recommended in patients with eGFR persistently (b) (4)
How Supplied	Segluromet (ertugliflozin and metformin hydrochloride) tablets are available in the strengths listed below: Segluromet tablets, 2.5 mg/500 mg, are pink, oval, film-coated tablets debossed with "2.5/500" on one side and plain on the other side. They are supplied as follows: NDC 0006-5369-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5369-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5369-03 unit-of-use bottles of 60 NDC 0006-5369-06 unit-of-use bottles of 180 NDC 0006-5369-07 bulk bottles of 500 Segluromet tablets, 2.5 mg/1000 mg, are pink, oval, film-coated tablets debossed with "2.5/1000" on one side and plain on the other side. They are supplied as follows: NDC 0006-5373-02 unit dose blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5373-05 unit-of-use blister packages of 30 (5 blister cards of 6 tablets) NDC 0006-5373-03 unit-of-use bottles of 60 NDC 0006-5373-06 unit-of-use bottles of 180 NDC 0006-5373-07 bulk bottles of 500 Segluromet tablets, 7.5 mg/500 mg are red, oval, film-coated tablets debossed with "7.5/500" on one side and

<table>
<tr><td></td><td>plain on the other side. They are supplied as follows:
NDC 0006-5370-02 unit dose blister packages of 30 (5 blister cards of 6 tablets)
NDC 0006-5370-05 unit-of-use blister packages of 30
(5 blister cards of 6 tablets)
NDC 0006-5370-03 unit-of-use bottles of 60
NDC 0006-5370-06 unit-of-use bottles of 180
NDC 0006-5370-07 bulk bottles of 500

Segluromet tablets, 7.5 mg/1000 mg are red, oval, film-coated tablets debossed with “7.5/1000” on one side and plain on the other side. They are supplied as follows:
NDC 0006-5374-02 unit dose blister packages of 30 (5 blister cards of 6 tablets)
NDC 0006-5374-05 unit-of-use blister packages of 30
(5 blister cards of 6 tablets)
NDC 0006-5374-03 unit-of-use bottles of 60
NDC 0006-5374-06 unit-of-use bottles of 180
NDC 0006-5374-07 bulk bottles of 500</td></tr>
<tr><td>Storage</td><td>Storage of Bottles
Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (between 59-86°F). Protect from moisture. Store in a dry place.

Storage of Blisters
Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (between 59-86°F). Store in the original package.</td></tr>
<tr><td>Container Closure</td><td>Commercial batches of Segluromet (ertugliflozin/metformin) tablets will be packaged in high density polyethylene (HDPE) bottles with desiccant and closures with heat induction seal liner.
Batches will also be packaged in aluminum/aluminum foil blister and lidding.

Blister System
<table>
<tr><th>Count</th><th>Blister Material</th><th>Lidding Material</th></tr>
<tr><td>1 per cell</td><td>Aluminum foil</td><td>Aluminum foil</td></tr>
</table>
HDPE Bottle/Closure System
<table>
<tr><th>Count</th><th>Bottle Size (Nominal)</th><th>Closure Size</th><th>Desiccant</th></tr>
<tr><td>14</td><td>75 mL</td><td>33 mm</td><td>1 gram</td></tr>
</table></td></tr>
</table>

	60	200 mL	38 mm	2 grams
	180	14 oz.	38 mm	3 grams
	500	40 oz.	43 mm	3 grams

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 11, 2017, we searched the L:drive and AIMS using the terms, Segluromet to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[b,c], and we confirmed that our previous recommendations were implemented or considered.

[b] Rychlik, I. Proprietary Name Review Memorandum for Segluromet NDA 209806. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 10. RCM No. 2017-12352891

[c]Rychlik, I. Proprietary Name Review for Segluromet IND122329. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 8 Panorama No. 2016-9231461.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Segluromet (ertugliflozin/metformin) labels and labeling submitted by Merck Sharp and Dohme Corp. on December 19, 2016.

- Container label
- Carton labeling
- Professional Sample Blistercards
- Professional Sample Carton Labeling
- Hospital Unit-Dose Blister labels
- Medication Guide
  \\cdsesub1\evsprod\nda209806\0000\m1\us\01-crt-usmg-mk8835b-t-original.doc

- Prescribing Information
  \\cdsesub1\evsprod\nda209806\0000\m1\us\01-crt-uspi-mk8835b-t-original.doc

G.2 Label and Labeling Images

1**. CONTAINER LABELS:**

(b) (4)

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

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

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

/s/

CASMIR I OGBONNA
05/04/2017

HINA S MEHTA
05/04/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209803

Application Type: New NDA

Drug Name(s)/Dosage Form(s): ertugliflozin tablets

Applicant: Merck Sharp & Dohme Corp.

Receipt Date: December 19, 2016

Goal Date: December 19, 2017

1. Regulatory History and Applicant's Main Proposals

On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for ertugliflozin tablet. Ertugliflozin tablet is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The proposed doses are 5 and 15 mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *Minor formatting edits needed to place the period outside the brackets. Section 6.1.*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ELIZABETH R GODWIN
03/01/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209805

Application Type: New NDA

Drug Name(s)/Dosage Form(s): ertugliflozin and sitagliptin tablets

Applicant: Merck Sharp & Dohme Corp.

Receipt Date: December 19, 2016

Goal Date: December 19, 2017

1. Regulatory History and Applicant's Main Proposals

On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for the combination product of ertugliflozin and sitagliptin tablet. Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin tablet, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. The proposed doses are (b) (4) 5/100; 15/100 mg/mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL length is greater than one-half page, no waiver has been granted in a previous submission as this is an original NDA submission.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional

Selected Requirements of Prescribing Information

• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A

13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *Minor formatting edits needed to place the period outside the brackets. Sections 1.1, 4, 5.6, 5.8, and 6.1.*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *A modified version of the above statement was included in section 6.2, "Postmarketing Experience."*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ELIZABETH R GODWIN
03/01/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209806

Application Type: New NDA

Drug Name(s)/Dosage Form(s): ertugliflozin and metformin hydrochloride tablets

Applicant: Merck Sharp & Dohme Corp.

Receipt Date: December 19, 2016

Goal Date: December 19, 2017

1. Regulatory History and Applicant's Main Proposals

On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for the combination product of ertugliflozin and metformin hydrochloride tablet. Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride tablet, a biguanide, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) The proposed doses are 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

This is a 505(b)(2) application that relies on the previous finding of safety and efficacy of NDA 020357, Glucophage (metformin hydrochloride) tablets.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL length is greater than one-half page, no waiver has been granted in a previous submission as this is an original NDA submission.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional

Selected Requirements of Prescribing Information

• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES

13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *Minor formatting edits needed to place the period outside the brackets. Sections 6.1, 8.5, 8.6, 12.3.*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH R GODWIN
03/01/2017

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 # 209803 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Steglatro (pending) Established/Proper Name: ertugliflozin Dosage Form: tablets Strengths: 5 mg and 15mg Route(s) of Administration: oral		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: 12/19/2016 Date of Receipt: 12/19/2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 12/19/2017	Action Goal Date (if different):	
Filing Date: 2/17/2017	Date of Filing Meeting: 1/30/2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 106447	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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 (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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)?	☒	☐	☐	
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 (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff*: For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Request for Proprietary name submitted January 4, 2017.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: QT/IRT study report consult 2/6/2017***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** December 17, 2012	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 6, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** September 8, 2011; December 19, 2013	☒			

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2017

BACKGROUND: On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for ertugliflozin tablet. Ertugliflozin tablet is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The proposed doses are 5 and 15 mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Liz Godwin	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	William Chong		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosebraugh		N
Clinical	Reviewer:	Frank Pucino	Y
	TL:	William Chong	Y
Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Alexander Cambon	Y
	TL:	Yun Wang	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Jessica Hawes	Y
	TL:	Ron Wange	Y
Statistics (safety)	Reviewer:	Elande Baro	Y
	TL:	Eugenio Andraca-Carrera	Y
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lamansingh	Y
• Drug Substance	Reviewer:	Erika Englund	N
• Drug Product	Reviewer:	Elise Luong	N
• Process	Reviewer:	Chaoying Ma	N
• Microbiology	Reviewer:	N/A	N/A
• Facility	Reviewer:	Allison Aldridge	N
• Biopharmaceutics	Reviewer:	Hansong Chen	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	Eric Duffy		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Charuni Shah	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Casmir Ogbonna	N
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Naomi Reed	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPMH	Reviewer: RPM:	Carrie Ceresa Denise Johnson-Lyles	N
	TL:	Miriam Dinatale	N
Other attendees	Sara Stradley (ADRA)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ 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? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Not needed at time of filing meeting, the drug is not the first in its class. ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The drug is not the first in its class
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**: Requested an Application Orientation Presentation with Applicant	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosebraugh **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 23, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): 74-day letter: March 3, 2017 Mid-Cycle Meeting: May 23, 2017 Mid-Cycle Communication: June 5, 2017 Labeling Planning Meeting: May 31, 2017 Complete Primary Review: August 19, 2017 Internal Late Cycle Meeting: August 24, 2017 Complete Secondary Review: August 26, 2017 Send labeling to Applicant: August 26, 2017 Late Cycle Meeting Background Package Due to Applicant: September 6, 2017 Late Cycle Meeting: September 18, 2017 Wrap-Up Meeting: October 25, 2017 CDTL Review: November 7, 2017 DD Review: November 14, 2017 ODE Review and Sign-off: November 28, 2017 PDUFA goal date: December 19, 2017 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

ELIZABETH R GODWIN
03/01/2017

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 # 209805 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Steglujan (pending) Established/Proper Name: ertugliflozin and sitagliptin Dosage Form: tablet Strengths: (b) (4) 5/100; 15/100 mg/mg Route(s) of Administration: oral		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: December 19, 2016 Date of Receipt: December 19, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: December 19, 2017	Action Goal Date (if different):	
Filing Date: February 17, 2017	Date of Filing Meeting: January 30, 2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): INDs 106447 and 122330	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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 (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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)?	☒	☐	☐	
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 (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff*: For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Request for Proprietary name submitted January 4, 2017.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 6, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2017

BACKGROUND: On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for the combination product of ertugliflozin and sitagliptin tablet. Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin tablet, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. The proposed doses are (b) (4) 5/100; 15/100 mg/mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Liz Godwin	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	William Chong		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosebraugh		Y
Clinical	Reviewer:	Frank Pucino	Y
	TL:	William Chong	Y
Clinical Pharmacology	Reviewer:	Lei He	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Alexander Cambon	Y
	TL:	Yun Wang	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Jessica Hawes	Y
	TL:	Ron Wange	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lamansingh	Y
• Drug Substance	Reviewer:	Erika Englund	N
• Drug Product	Reviewer:	Ravindra Kasliwal	N
• Process	Reviewer:	Huai (Ted) Chang	N
• Microbiology	Reviewer:	N/A	N/A
• Facility	Reviewer:	Krishna Ghosh	N
• Biopharmaceutics	Reviewer:	Peng (Vincent) Duan	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	James Laurenson (EA reviewer) Eric Duffy (BC)		N Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Charuni Shah	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Casmir Ogbonna	Y
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Naomi Reed	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
DPMH	Reviewer: RPM:	Carrie Ceresa Denise Johnson-Lyles	N
	TL:	Miriam Dinatale	N
Other attendees	Sara Stradley (ADRA)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ 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? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Not needed at time of filing meeting, the drug is not the first in its class. ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The drug is not the first in its class
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**: Categorical exclusion and Environmental Assessment was included in the application	☒ YES ☐ NO ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Curtis Rosebraugh **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 23, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): 74-day letter: March 3, 2017 Mid-Cycle Meeting: May 23, 2017 Mid-Cycle Communication: June 5, 2017 Labeling Planning Meeting: May 31, 2017 Complete Primary Review: August 19, 2017 Internal Late Cycle Meeting: August 24, 2017 Complete Secondary Review: August 26, 2017 Send labeling to Applicant: August 26, 2017 Late Cycle Meeting Background Package Due to Applicant: September 6, 2017 Late Cycle Meeting: September 18, 2017 Wrap-Up Meeting: October 25, 2017 CDTL Review: November 7, 2017 DD Review: November 14, 2017 ODE Review and Sign-off: November 28, 2017 PDUFA goal date: December 19, 2017 **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

ELIZABETH R GODWIN
03/01/2017

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 # 209806 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Segluromet (pending) Established/Proper Name: ertugliflozin and metformin hydrochloride Dosage Form: tablet Strengths: 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg Route(s) of Administration: oral		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: December 19, 2016 Date of Receipt: December 19, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: December 19, 2017	Action Goal Date (if different):	
Filing Date: February 17, 2017	Date of Filing Meeting: January 30, 2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted] (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): INDs 106447 and 122329	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• 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)].**	☐	☒		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☒		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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 (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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)?	☒	☐	☐	
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 (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff*: For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☒	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Request for Proprietary name submitted January 4, 2017.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 6, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2017

BACKGROUND: On December 19, 2016, Merck Sharp & Dohme Corporation, submitted this New Drug Application (NDA) for the combination product of ertugliflozin and metformin hydrochloride tablet. Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride tablet, a biguanide, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) The proposed doses are 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg. This is a New Molecular Entity (NME), type 1 NDA with a Prescription Drug User Fee Act (PDUFA) goal date of December 19, 2017.

This is a 505(b)(2) application that relies on the previous finding of safety and efficacy of NDA 020357, Glucophage (metformin hydrochloride) tablets.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Liz Godwin	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	William Chong		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosebraugh		N
Clinical	Reviewer:	Frank Pucino	Y
	TL:	William Chong	Y
Clinical Pharmacology	Reviewer:	Lei He	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Alexander Cambon	Y
	TL:	Yun Wang	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Jessica Hawes	Y
	TL:	Ron Wange	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lamansingh	Y
• Drug Substance	Reviewer:	Erika Englund	N
• Drug Product	Reviewer:	Elise Luong	N
• Process	Reviewer:	Hong Yang	N
• Microbiology	Reviewer:		
• Facility	Reviewer:	Michael Klapal	N
• Biopharmaceutics	Reviewer:	Kalpana Paudel	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Eric Duffy		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Shawna Hutchins	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Charuni Shah	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Casmir Ogbonna	Y
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Naomi Reed	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPMH	Reviewer: RPM:	Carrie Ceresa Denise Johnson-Lyles	N
	TL:	Miriam Dinatale	N
Other attendees	Sara Stradley (ADRA)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ 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? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Not needed at time of filing meeting, the drug is not the first in its class. ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The drug is not the first in its class
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Curtis Rosebraugh **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 23, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): 74-day letter: March 3, 2017 Mid-Cycle Meeting: May 23, 2017 Mid-Cycle Communication: June 5, 2017 Labeling Planning Meeting: May 31, 2017 Complete Primary Review: August 19, 2017 Internal Late Cycle Meeting: August 24, 2017 Complete Secondary Review: August 26, 2017 Send labeling to Applicant: August 26, 2017 Late Cycle Meeting Background Package Due to Applicant: September 6, 2017 Late Cycle Meeting: September 18, 2017 Wrap-Up Meeting: October 25, 2017 CDTL Review: November 7, 2017 DD Review: November 14, 2017 ODE Review and Sign-off: November 28, 2017 PDUFA goal date: December 19, 2017 **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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/s/

ELIZABETH R GODWIN
03/01/2017

M E M O R A N D U M

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

DATE: February 17, 2017

TO: Geoff Kim, M.D.
Director
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products

Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II (ODEII)

FROM: Xikui Chen, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sally Choe, Ph.D.
Deputy Director
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of inspection of (b) (4), (b) (4), covering (b) (4) (b) (4) NDA 209803 (ertugliflozin)

Summary:
The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4) (b) (4), covering the analytical portion of bioequivalence studies under NDA (b) (4) 209803. No significant deficiencies were observed and Form FDA 483 was not issued at the close of the inspection. The final classification of the inspection is No Action Indicated (NAI). Based on the inspection findings, these reviewers recommend that data from the following studies be accepted for further Agency review.

Table 1.

NDA	Study #	Study title	Clinical Study Dates	Analytical Study Dates
[redacted]				
209803	B1521037	"A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 15 mg Commercial Image Tablet vs Ertugliflozin Phase 3 Tablets in Healthy Subjects"	April 24, 2015 (First patient enrolled) to June 03, 2015 (Last patient completed)	June 06, 2015 to June 15, 2015

OSIS investigators, Seongeun (Julia) Cho and Xikui Chen, conducted an audit of [redacted]

The audit of the studies listed in **Table 1** included a thorough review of method validations, study records, facility equipment, and original laboratory worksheets, and interviews with the firm's management and staff.

Conclusion:

Based on the inspectional findings and overall evaluation of bioanalytical study conduct at [redacted], the OSIS reviewers conclude that data from the studies listed in Table 1 are reliable. Therefore, these reviewers recommend that the analytical portion of the studies listed in Table 1 be accepted

for further Agency review.

Final Site Classification:

NAI
FEI: [redacted]

DARRTS CC:
OTS/OSIS/Kassim/Choe/Taylor/Haidar/Miller/Nkah/Kadavil
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
CDER/OND/Kim/Farrell/Guettier
Draft: XC 2/16/17
Edits: MFS 2/17/2017; JC 2/17/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL SITES/[redacted]

OSI file #: [redacted] BE7382 (NDA 209803)
FACTS: [redacted]

Xikui Chen, Ph.D.
OSIS, DGDBE

Sally Choe, Ph.D.
Deputy Director
OSIS

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/s/

XIKUI CHEN
02/17/2017

SEONGEUN CHO
02/17/2017

SALLY Y CHOE
02/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: Zhihong Li, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
REVIEW DATE: 6/27/2014	IND No.: 122329 Serial No.:	NDA No.	SUBMISSION DATE : 5/9/2014	
NAME OF DRUG: FDC of ertugliflozin/metformin (MK-8835B)	PRIORITY CONSIDERATION Standard		Date of informal/Formal Consult:	
NAME OF THE SPONSOR: Merck Sharp & Dohme Corp.				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY RELATED ISSUE

☒ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PHASE I PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (PIND)	☐ OTHER *(SPECIFY BELOW):*
☐ PHASE IV RELATED		[]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

(b) (4)

[redacted]

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/s/

ZHIHONG LI
07/22/2014

LOKESH JAIN
07/22/2014