

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204353Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204353	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: TBD		
Established/Proper Name: canagliflozin and metformin hydrochloride immediate release		
Dosage Form: Tablet		
Strengths: 50/500 mg, 50/1000 mg, 150/500 mg, and 150/1000 mg		
Applicant: Janssen Pharmaceuticals, Inc		
Date of Receipt: 12/12/12 (original NDA); 2/10/2014 (resubmission following CR)		
PDUFA Goal Date: 8/10/2014		Action Goal Date (if different): 8/8/2014
RPM: Abolade (Bola) Adeolu		
Proposed Indication(s): Treatment of type 2 diabetes mellitus		

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)
Literature references	
NDA 020357 (Glucophage)	FDA's previous finding of safety and effectiveness, Nonclinical pharmacology, Nonclinical pharmacokinetics, Nonclinical toxicology, Nonclinical literature references, Clinical studies, Clinical studies report and related information, and USPI metformin labeling text.

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

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

In the initial round, the phase 1 study (DIA1032) was not sufficient to bridge efficacy findings between canagliflozin dosed once daily with canagliflozin dosed twice daily. Following resubmission, the Modeling and simulation strategy was utilized to bridge efficacy between QD and BID dosing regimens for canagliflozin to support approval of canagliflozin/metformin fixed dose combination (FDC) product for treatment of adult patients with type 2 diabetes. Exposure-response analysis was used to demonstrate that the efficacy of canagliflozin is similar following QD or BID dosing regimen.

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 without the published literature)?

YES X 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 X NO

If “NO”, proceed to question #5.

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

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

YES X NO

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 X 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	020357	Y

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 X 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 X

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-dose combination of canagliflozin 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):

- 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): Applicant holds all patents
- (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): *Applicant is patent holder*

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/

ABOLADE ADEOLU
08/08/2014

PMR/PMC Development Template

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

NDA/BLA # NDA 204353
Product Name: Invokamet (canagliflozin and metformin hydrochloride) fixed-dose combination tablets

PMR/PMC Description: A study to evaluate whether pediatric patients with type 2 diabetes ages 10 to 17 years (inclusive) or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Invokamet tablets. The study should evaluate tablets that are the same dimensions as the largest Invokamet tablet, and placebo tablets should be used if the study population consists of healthy subjects.

PMR/PMC Schedule Milestones: Final Protocol Submission: May 2015
Study/Trial Completion: May 2017
Final Report Submission: November 2017

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

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

Invokamet is ready for approval for use in adults; however, pediatric studies had been deferred.

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

The goal of this study is to study whether pediatric patients 10 to 17 years (inclusive) can swallow the fixed dose combination (FDC) tablets safely.

The FDC tablets are larger than the individual canagliflozin and metformin tablets, with the largest FDC tablet having the following dimensions: length 22.1 mm, width 11.1 mm, thickness 8.8 mm. This large size may present a choking risk in pediatric patients. The PMR addresses this potential risk by requiring the applicant to characterize the swallowability of the FDC tablets in the pediatric population aged 10 to 17 years (inclusive).

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The study will be a swallowability study of the FDC tablets. The study population may consist of either pediatric patients with type 2 diabetes mellitus ages 10 to 17 years (inclusive) or healthy pediatric subjects ages 10 to 17 years (inclusive). The study will evaluate tablets that are the same dimensions as the largest Invokamet tablet, and placebo tablets should be used if the study population consists of healthy subjects.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Pediatric swallowability study.
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

JENNIFER R PIPPINS
08/07/2014

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

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

Memorandum

Date: August 5, 2014

To: Abolade Adeolu, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Subject: NDA 204353
OPDP labeling comments for INVOKAMET™ (canagliflozin and metformin hydrochloride) tablets for oral use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labels for INVOKAMET™ (canagliflozin and metformin hydrochloride) tablets for oral use (Invokamet) submitted for consult on February 20, 2014.

Prescribing Information

OPDP's comments on the proposed draft PI are based on the version sent from Abolade Adeolu (RPM) on July 25, 2014, and are provided directly on the marked version below.

Carton/Container Labels

OPDP has no comments regarding the proposed draft carton/container labels sent from Abolade Adeolu on August 1, 2014.

Medication Guide

OPDP's comments on the proposed draft medication guide were provided under separate cover in conjunction with Division of Medical Policy Programs (DMPP) on August 1, 2014.

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

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

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

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/s/

KENDRA Y JONES
08/05/2014

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

PATIENT LABELING REVIEW

Date: August 1, 2014

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endrocrinology Products (DMEP)

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

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

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): INVOKAMET (canagliflozin and metformin hydrochloride)

Dosage Form and Route: tablets

Application Type/Number: NDA 204353

Applicant: Janssen Research & Development, LLC.

1 INTRODUCTION

On December 12, 2012, Janssen Research & Development, LLC. submitted for the Agency's review an Original New Drug Application for canagliflozin and metformin hydrochloride immediate release tablets. On December 11, 2013, the Agency issued a Complete Response (CR) action regarding lack of clinical data and studies supporting the bridge from once daily to twice daily dosing. On February 10, 2014, the applicant resubmitted the application for approval. INVOKAMET, the TRADENAME for canagliflozin and metformin hydrochloride is a combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus who are not necessarily adequately controlled on a regimen containing metformin or canagliflozin.

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 February 20, 2014 and February 21, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INVOKAMET (canagliflozin and metformin hydrochloride) tablets

2 MATERIAL REVIEWED

- Draft INVOKAMET (canagliflozin and metformin hydrochloride) MG received on February 10, 2014 and received by DMPP on July 25, 2014.
- Draft INVOKAMET (canagliflozin and metformin hydrochloride) MG received on February 10, 2014, and received by OPDP on July 25, 2014.
- Draft INVOKAMET (canagliflozin and metformin hydrochloride) Prescribing Information (PI) received on February 10, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on July 25, 2014.
- Draft INVOKAMET (canagliflozin and metformin hydrochloride) Prescribing Information (PI) received on February 10, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on July 25, 2014.
- Approved INVOKANA (canagliflozin) comparator labeling dated June 6, 2014.

3 REVIEW METHODS

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

In our collaborative review of the MG we have:

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

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
08/01/2014

KENDRA Y JONES
08/01/2014

MELISSA I HULETT
08/01/2014

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: March 28, 2014

Requesting Office or Division: Division of Metabolism and Endocrinology (DMEP)

Application Type and Number: NDA 204353

Product Name and Strength: Invokamet (canagliflozin and metformin HCl) tablets,
50 mg/500 mg, 50 mg/1,000 mg, 150 mg/500 mg,
150 mg/1,000 mg

Product Type: Combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Janssen, LLC

Submission Date: March 13, 2014

OSE RCM #: 2014-377

DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels and prescribing information for Invokamet (canagliflozin and metformin HCl) tablets, NDA 204353, submitted on March 13, 2014, for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling and determined that there are no significant concerns. Thus, usual recommendations on increasing readability and prominence of important information on the proposed labels and labeling will be made.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and mitigate any potential confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

- A. Section 17 Patient Counseling Information in Full Prescribing Information:

1. Include the warning statement “Store in original container” as an instruction for patients to increase awareness to the importance of not removing Invokamet tablets from the original container or transferring to a pill box as such actions may affect the product’s stability. Suggested language may include: “Instruct patients to keep Invokamet in the original bottle to protect from moisture. Do not put Invokamet in pill boxes or pill organizers.”

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

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

A. Container label

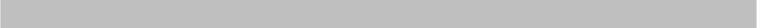
1. Relocate the warning statement “Store in the original container” to the principal display panel of the label and increase the size and prominence per Guidance: Container Labels and Carton Labeling, April 2013.¹ Relocating this warning statement may increase awareness to the importance of not removing Invokamet tablets from the original container or transferring to a pharmacy bottle or pill box since such actions may affect the product’s stability. As currently presented, this warning statement can be overlooked, which may impact the stability of the product.

If you have further questions or need clarification, please contact Lyle Canida, OSE Project Manager, at 301-796-1637.

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Invokamet that Janssen, LLC submitted on March 13, 2014.

Table 2. Relevant Product Information for Invokamet	
Active Ingredient	Canagliflozin and metformin HCl Immediate Release tablets
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin. Invokamet can also be used in patients who are already treated with both canagliflozin and metformin.
Route of Administration	Oral
Dosage Form	Tablets
Strength	<ul style="list-style-type: none"> • 50 mg canagliflozin and 500 mg metformin hydrochloride • 50 mg canagliflozin and 1,000 mg metformin hydrochloride • 150 mg canagliflozin and 500 mg metformin hydrochloride • 150 mg canagliflozin and 1,000 mg metformin hydrochloride
Dose and Frequency	<ul style="list-style-type: none"> • Individualize based on the patient’s current regimen. •  (b) (4) •  • 
How Supplied	<ul style="list-style-type: none"> • 50 mg canagliflozin and 500 mg metformin HCl: immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side; 60-count  (b) (4) bottles • 50 mg canagliflozin and 1,000 mg metformin HCl:

	<p>immediate-release, capsule-shaped, beige film-coated tablets with “CM” on one side and “551” on the other side; 60-count (b) (4) bottles</p> <ul style="list-style-type: none"> • 150 mg canagliflozin and 500 mg metformin HCl: immediate-release, capsule-shaped, yellow film-coated tablets with “CM” on one side and “215” on the other side; 60-count (b) (4) bottles • 150 mg canagliflozin and 1,000 mg metformin HCl: immediate-release, capsule-shaped, purple film-coated tablets with “CM” on one side and “611” on the other side; 60-count (b) (4) bottles
Storage	Store at 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F). Store in the original container.
Container Closure	<ul style="list-style-type: none"> • (b) (4) bottle with (b) (4), induction seal, and desiccant • (b) (4) bottle with (b) (4), induction seal, and desiccant • (b) (4) bottle with (b) (4), induction seal, and desiccant • (b) (4) with (b) (4), induction seal, and desiccant

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched an internal FDA database on February 27, 2014 using the term, Invokamet to identify reviews previously performed by DMEPA.

B.2 Results

DMEPA had previously reviewed the proposed container labels and prescribing information for Invokamet in OSE Review # 2013-160 on September 17, 2013.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Invokamet labels and labeling submitted by Janssen on March 13, 2014.

- Container labels
- Prescribing Information
- Medication Guide

C.2 Label and Labeling Images

Container Labels

(b) (4)

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

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

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/s/

MISHALE P MISTRY
03/28/2014

YELENA L MASLOV
03/28/2014

MEMORANDUM

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

DATE: February 21, 2013

TO: Branch Chief,
Medical Products & Tobacco Trip Planning Branch
(MPTTPB)
Division of Medical Products and Tobacco Inspections
(DMPTI)
Office of Medical Products and Tobacco Operations
(OMPTO)

Director, Investigations Branch
Kansas District Office (KAN-DO)
11630 W. 80th St.
Lenexa, KS 66214

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2013, High Priority, User Fee Pre-Approval Data
Validation Inspection** Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 204-353
DRUG: Canagliflozin/Metformin immediate
release fixed dose combination tablet
SPONSOR: Janssen Research and Development

This memo requests that you arrange for inspection of the clinical and analytical portions of the following pharmacokinetic and bioequivalence studies. A DBGLPC scientist with specialized knowledge will participate in the analytical site inspection to provide scientific and technical expertise.

Please contact DBGLPC upon receipt of this assignment to arrange scheduling of the inspection. Following identification of the investigator, background material will be forwarded directly.

This inspection should be completed by September 1, 2013 to meet the PDUFA review due date.

DO NOT identify the studies to be inspected, the drug names, or the study investigators prior to the start of the inspection. The information will be provided to the sites at the inspection opening meetings.

At the completion of inspection, please send a scanned copy of the completed sections A & B to Dr. Sam Haidar and the DBGLPC POC.

Study #1: 28431754DIA1032
Study Title: An Open-Label, Multiple-Dose Study to Assess the Steady-State Pharmacokinetics, Pharmacodynamics and Safety of Once-Daily Versus Twice-Daily Dosing With Canagliflozin in Healthy Subjects

Study #2: 28431754DIA1038
Study Title: A Single-Dose, Open-Label, Randomized, 2-Way Crossover Pivotal Study to Assess the Bioequivalence of 2 Fixed Dose Combination Tablets of Canagliflozin and Metformin Immediate Release (IR) (150 mg/1,000 mg) With Respect to the Individual Components of Canagliflozin (1 x 300 mg) and Metformin IR Tablets (2 x 1,000 mg) in Healthy Fed Subjects

Clinical Site#1: Quintiles Phase One Services,
(Study #1) 6700 W. 115th Street, Overland Park, KS
66211), USA
FEI Number: Not Available

Contact: David R. Mathews, MD
TEL: +1-(913) 894-5533
david.mathews@quintiles.com

Clinical Site #2: Celerion, Inc.
(Study #2) 621 Rose Street, Lincoln,
NE 68502
FEI Number: 1915582

Contact: Stephen Youngberg, MD
+1(402)476-2811
stephen.youngberg@celerion.com

SECTION A

RESERVE SAMPLES: Study 28431754DIA1038 (Study #2) is a bioequivalence study subject to 21 CFR 320.38 and 320.63, and the site conducting the study is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>). Please refer to CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- Please obtain a written assurance from the Investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, remained in custody of the Investigator or responsible person at the site, and were stored under conditions specified in accompanying records. Document the signed and dated statement [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the alternative site is independent from the sponsor, packager or the manufacturer, and that the sponsor was notified in writing of the location. In an event reserve samples are not retained or not adequate in quantity; please notify the DBGLPC POC immediately.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Benjamin (Nick) Westenberger, Ph.D.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314)539-3869

Please note that **Study 28431754DIA1032 (Study #1) is not a bioequivalence study** and reserve samples collection is not required.

SECTION B

Please confirm the informed consent and records for 100% of subjects enrolled at the site. The study records in the NDA submission should be compared to the original documents at the site. Include a description of your findings in the EIR.
Data Audit Checklist

- Evidence of under-reporting of AEs identified? _____
- Evidence of inaccuracy in electronic data capture? _____
- Presence of 100% of signed and dated informed consent forms: _____
- Reports for the subjects audited: _____
- Number of subject records reviewed during the inspection: _____
- Number of subjects screened at the site: _____
- Number of subjects enrolled at the site: _____
- Number of subjects completing the study: _____
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms: _____
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol: _____
- Confirm that SOPs were followed during study conduct: _____
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports: _____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, case report forms for dosing, and whether the randomization schedule was followed for dosing of subjects, etc.)

- Other Comments:
-
-

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Analytical Site:



Contact Person:



Methodology:

LC/MS-MS

Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of canagliflozin/metformin concentrations in human plasma should be examined.
- The accuracy of analytical data provided by the sponsor in the NDA submissions should be compared with the original documents at the site.
- The method validation and the actual assay of the subject plasma samples, the variability between and within runs, demonstration of at least one accuracy and precision in matrix using standards and QCs prepared from separate stocks, QC accuracy and precision during sample analysis, subject samples were analyzed within the established storage stability.
- Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like

Page 6 - BIMO Assignment, NDA 204-353, Canagliflozin/Metformin immediate release fixed dose combination tablet

freeze thaw cycles sufficiently covered stability of reanalyzed subject samples.

In addition to the standard investigation involving the source documents, the files of correspondence between the analytical sites and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions and questions may be provided by DBGLPC prior to commencing the inspection. Therefore, we request that the DBGLPC POC be contacted for any further follow-up instructions before the inspection and also regarding any data anomalies noted during review of study report. The ORA investigator should contact the DBGLPC Point of Contact (POC) for inspection related questions or clarifications.

Please FAX/Email a copy of Form FDA-483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA-483. Please forward written response as soon as you receive it to Dr. Sam Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC POC:

Arindam Dasgupta, Ph.D.
(301) 796-3326

Email: arindam.dasgupta@fda.hhs.gov

Page 7 - BIMO Assignment, NDA 204-353, Canagliflozin/Metformin
immediate release fixed dose combination tablet

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Dasgupta/Dejernett/CF

HFC-130/ORAHQ OMPTO DMPTI BIMO

ORA/ORO/DFFI/IOB/Turner/Arline/Montemurro

OND/ODEII/DMEP/Adeolu

OCP/DCP2/Sahajwalla/Jain

ORA/SW-FO/KAN-DO/KAN-IB/Bromley

ORA/SW-FO/KAN-DO/STL-MO/Bous

Draft: AD 02/21/2013

Edit: MFS 2/22/13

OSI: BE6428; O:\BE\assigns\bio204353.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1498290

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/s/

ARINDAM DASGUPTA
02/25/2013

WILLIAM H TAYLOR
02/25/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204353

Application Type: New NDA

Name of Drug: canagliflozin and metformin HCl immediate release tablets

Applicant: Janssen Pharmaceuticals, Inc.

Submission Date: 12/12/12

Receipt Date: 12/12/12

1.0 Regulatory History and Applicant's Main Proposals

Canagliflozin and metformin HCl immediate release tablet is a sodium-glucose cotransporter (SGLT2) inhibitor intended to be used to treat T2DM. The proposed doses are 50/500, 50/1000, 150/500, and 150/1000mg. Janssen Pharmaceuticals, Inc. submitted the NDA on December 12, 2013. This is an NME, type 4 NDA and PDUFA goal date is December 12, 2013.

This is a 505(b)(2) application that relies on the previous finding of safety and efficacy of Glucophage NDA 020357. The NDA also references NDA 204042 (canagliflozin), which is currently under review with a PDUFA goal date of March 31, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Length of HL greater than 0.5 page*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• 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 the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- NO** 12. All text must be **bolded**.
Comment:
- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- NO** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** 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

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Issued :MM/YY instead of Revised:MM/YY*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

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:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Some are see[Dosage Forms and Strength (3)]....the word see has to be in the box for example 2.1*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.

Comment: *All text is not bolded*

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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 clinical practice.”

Comment: 'trials' replaced with 'studies'

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), 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

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ABOLADE ADEOLU
02/20/2013

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 # 204353	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: canagliflozin and metformin HCl immediate release Dosage Form: Tablet Strengths: 50/500, 50/1000, 150/500, and 150/1000 mg		
Applicant: Janssen Pharmaceuticals Inc. Agent for Applicant (if applicable):		
Date of Application: 12/12/12 Date of Receipt: 12/12/12 Date clock started after UN:		
PDUFA Goal Date: 12/12/13		Action Goal Date (if different):
Filing Date: 2/10/13		Date of Filing Meeting: 1/24/13
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 (NME) and Type 4 (new combination)		
Proposed indication(s)/Proposed change(s): Treatment of type 2 diabetes mellitus (T2DM)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 076479 (canagliflozin) and IND 110545 (canagliflozin+metformin IR FDC)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			(b) (4)
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2	X			

1

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

(BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		X		
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			

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

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Applicant plans to submit 2 nd quarter 2013
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

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

4

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		X		4/25/12 meeting request denied, written responses sent 8/30/2012.
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 24, 2013

NDA: 204353

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: canagliflozin and metformin HCl immediate release tablet

DOSAGE FORM/STRENGTH: 50/500, 50/1000, 150/500, and 150/1000 mg

APPLICANT: Janssen Pharmaceuticals Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of type 2 diabetes mellitus (T2DM)

BACKGROUND: Canagliflozin and metformin HCl immediate release tablet is a sodium-glucose cotransporter 2 (SGLT2) inhibitor intended to be used to treat T2DM. The proposed doses are 50/500, 50/1000, 150/500, and 150/1000mg. Janssen Pharmaceuticals, Inc. submitted the NDA on December 12, 2013. This is an NME, type 4 NDA and PDUFA goal date is December 12, 2013.

This is a 505(b)(2) application that relies the previous finding of safety and efficacy of Glucophage NDA 020357. The NDA also references NDA 204042 (canagliflozin), which currently under review with a PDUFA goal date of March 31, 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Abolade (Bola) Adeolu	Y
	CPMS/TL:	Julie Marchick	Y
Cross-Discipline Team Leader (CDTL)	Jean-Marc Guettier		Y
Clinical	Reviewer:	Hyon (KC) Kwon	Y
	TL:	Jean-Marc Guettier	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC</i>	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Lokesh Jain	Y
Biopharm	Reviewer:	Okpo Eradiri	Y
	TL:	Angelica Dorantes	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fred Alavi	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	Wei Liu	Y
	TL:	Todd Sahlroot	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shelly Markofsky	Y
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Cynthia Kleppinger	N
	TL:	Janice Pohlman	Y
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Steve Hertz, OC/OMPQ		Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p> <p><u>Clinical Pharmacology</u> You have indicated that the tablet formulations used in the study DIA2003 are linked to the to-be marketed canagliflozin/metformin immediate release fixed dose combination (CANA/MET IR FDC) tablets through the PK bioequivalence between twice-daily and once- daily administered tablets assessed in the study DIA1032. Adequacy of this bridging will be a review issue.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, explain:</p>	
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Drug will not be first in class after approval of NDA 204042 (canagliflozin) on 3/31/2013
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOPHARM</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	X Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Mary H. Parks, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 14, 2013	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

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

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

ABOLADE ADEOLU
02/20/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 17, 2013

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Invokamet (Canagliflozin and Metformin HCl),
50 mg/500, 50 mg/1000 mg, 150 mg/500 mg, and
150 mg/1000 mg

Application Type/Number: NDA 204353

Applicant/sponsor: Janssen, LLC

OSE RCM #: 2013-160

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION.....	1
1.1	Background	1
1.2	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED	1
3	CONCLUSIONS	2
4	RECOMMENDATIONS.....	2
	Appendices.....	4

1 INTRODUCTION

This review evaluates the proposed container label and inserts labeling for Invokamet (Canagliflozin and Metformin HCl) NDA 204353 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant submitted the proposed container label, carton and insert labeling for the proposed proprietary name, Invokana on August 15, 2013.

1.2 PRODUCT INFORMATION

- Active Ingredient: Canagliflozin and Metformin HCl
- Indication of Use: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 50 mg/500, 50 mg/1000 mg, 150 mg/500 mg, and 150 mg/1000 mg
- Dose and Frequency: (b) (4) twice daily.
- How Supplied: (b) (4) bottles; (b) (4)
- Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). Store in the original container.
- Container and Closure Systems:
 - (b) (4), induction seal, and desiccant
 - (b) (4), induction seal, and desiccant
 - (b) (4), induction seal, and desiccant
 - (b) (4), induction seal, and desiccant

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted August 15, 2013 (Appendix A)
- Professional Sample Container Label submitted August 15, 2013 (Appendix B)
- Insert Labeling submitted August 15, 2013 (not included)

3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4 RECOMMENDATIONS

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

A. Insert Labeling

1. Under Dosage Forms and Strengths in the Highlights of Prescribing Information, Section 2 Dosage and Administration and Section 3 Dosage Forms and Strengths in the Full Prescribing Information, replace the slash symbol “/” used between the two ingredients with the word “and.” For example, revise “50 mg canagliflozin/500 mg metformin hydrochloride” with “50 mg canagliflozin **and** 500 mg metformin hydrochloride

B. Container Label

1. Revise the color scheme used to highlight and differentiate the strength statements. As currently presented, the strengths are not well differentiated and may cause product selection errors due to proximity in storage and similarity in trade dress:
 - i. For the 50 mg/500 mg strength, add color intensity to increase the prominence of that strength. As currently presented, the strength presentation is the same color as the proprietary name and established name and the box around the strength is barely visible, making it difficult to distinguish the strength of the product.
 - a. Revise the color scheme used to highlight the strength presentation of the 50 mg/1000 mg ((b) (4)) and 150 mg/500 mg ((b) (4)) to provide adequate differentiation. As currently presented the colors are similar and may cause product selection errors due to proximity in storage and similarity in trade dress.
 - ii. Revise the color scheme used to highlight the strength presentation of the 150 mg/1000 mg ((b) (4)) because this (b) (4) is the same color used for (b) (4). Ensure that the color scheme is not similar to any of the other color already used for (b) (4)

2. Relocate the statement “Each tablet contains xx mg Canagliflozin and xx mg metformin hydrochloride” currently on the principal display panel (PDP) to the side panel to reduce clutter on the PDP.
3. Ensure that the image of the tablet accurately represents the actual size, shape, color, and imprint of the commercial tablet and is not a schematic or computer-generated shape or image. In addition, this image should be less prominent and located away from important information such as proprietary name, established name and strength.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

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/s/

REASOL AGUSTIN
09/17/2013

YELENA L MASLOV
09/17/2013

MEMORANDUM

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

DATE: September 16, 2013

TO: Mary Parks, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Division of Bioequivalence and GLP Compliance
(DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering Canagliflozin/Metformin
immediate release fixed dose combination tablet,
sponsored by Janssen Research and Development

At the request of the Division of Metabolism and Endocrinology Products, Office of New Drugs, DBGLPC audited the clinical and analytical portions of the following pharmacokinetic and bioequivalence studies.

Study #: 28431754DIA1032
Study Title: An Open-Label, Multiple-Dose Study to Assess the Steady-State Pharmacokinetics, Pharmacodynamics and Safety of Once-Daily versus Twice-Daily Dosing with Canagliflozin in Healthy Subjects

Study #: 28431754DIA1038
Study Title: A Single-Dose, Open-Label, Randomized, 2-Way Crossover Pivotal Study to Assess the Bioequivalence of 2 Fixed Dose Combination Tablets of Canagliflozin and Metformin Immediate Release (IR) (150 mg/1,000 mg) with Respect to the Individual Components of Canagliflozin (1 x 300 mg) and Metformin IR Tablets (2 x 1,000 mg) in Healthy Fed Subjects

The clinical portions of the studies were audited at Quintiles Phase One Services, Overland Park, KS (8/26-8/29/2013 by ORA Investigator Carmen Fisher) and Celerion, Inc., Lincoln, NE (8/7-8/9/2013 by ORA Investigator Ismael Olvera). Th

(b) (4)

The audit included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

Following the inspections at the clinical sites no Form FDA-483 was issued and there were no significant findings at either site. Following inspection of the analytical site, For (b) (4) -483 was issued (**Attachment 1**). DBGLPC received (b) (4) response to the inspectional findings (b) (4) (**Attachment 2**)

The Form FDA-483 observations for studies 28431754DIA1032 (b) (4) 8431754DIA1038 and its associated method validation, (b) (4) response, and my evaluation follow:

Analytical Site : (b) (4)

(b) (4)

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Conclusions:

Following review and evaluation of the EIRs and the Form FDA-483 observations and the response from the analytical site, in my opinion, the clinical and analytical data generated from studies 28431754DIA1032 and 28431754DIA1038 were not affected by the cited observations. I recommend that data for clinical and analytical portions of studies 28431754DIA1032 and 28431754DIA1038 should be accepted for further agency review.

**Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC, OSI**

Final Classifications:

Clinical

NAI: Quintiles Phase One Services, Overland Park, KS

NAI: Celerion, Inc., Lincoln, NE

Analytical

VAI:

(b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Choi/Bonapace/Dasgupta/Dejernett/CF

OND/ODEII/DMEP/Parks/Adeolu

OCP/DCP2/Sahajwalla/Jain

ORA/SW-FO/KAN-DO/KAN-IB/Bromley

ORA/SW-FO/KAN-DO/KAN-IB/Fisher

ORA/SW-FO/KAN-DO/KAN-IB/OMAH-NE/Olvera

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Edit: MFS 9/11/2013

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/s/

ARINDAM DASGUPTA
09/16/2013

MICHAEL F SKELLY
09/16/2013
Skelly signing on behalf of Dr. Haidar

WILLIAM H TAYLOR
09/17/2013