CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s032

OTHER REVIEW(S)

Memorandum of Consultation

DATE:	May 28, 2019
FROM:	Michelle Carey, MD, MPH Medical Officer Division of Metabolism and Endocrinology Products (DMEP)
THROUGH:	Patrick Archdeacon, MD Acting Clinical Team Leader, DMEP Lisa Yanoff, MD Director (Acting), DMEP
TO:	Anna Park Regulatory Project Manager Division of Cardiovascular and Renal Products (DCRP)
SUBJECT:	Proposed labeling changes (b) (4) submitted to NDA 204042 S-32, (b) (4) (b) (4)

I. Background

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), and to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular (CV) disease. On March 27, 2019, Janssen Pharmaceuticals submitted (b) (4) INVOKANA/canagliflozin (NDA 204042 (b) (4) The (b) (4) data from the "**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation" trial (**CREDENCE**), intended to support the proposed indication (b) (4)

Briefly, CREDENCE was an event-driven trial with a planned duration of 5 to 5.5 years and a target of 844 primary efficacy endpoint events (a composite endpoint of doubling of serum creatinine, ESKD, renal or CV death). Enrolled patients were adults ≥30 years with T2DM who had diabetic kidney disease, an eGFR ≥30 to <90 mL/min/1.73m2, albuminuria defined by a urinary albumin/creatinine ration (UACR) >300 to ≤5000 mg/g, and were taking the maximum tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) for at least 4 weeks prior to enrollment. Overall 4,401 subjects were randomized: 2,202 to canagliflozin and 2,199 to placebo. A prespecified interim analysis of the

study was performed after 413 subjects had a confirmed event that was a component of the primary composite efficacy endpoint, as determined by the Endpoint Adjudication Committee. The results of the interim analysis were overwhelmingly favorable to canagliflozin, such that the predefined stopping rules for efficacy were met, and the Independent Data Monitoring Committee recommended that the study be stopped early. The mean duration of follow-up in CREDENCE was 2.6 years, or approximately half the duration originally planned for the trial.

The adequacy of the CREDENCE data to support the Applicant's proposed new indication (b) (4) (b) (4) is currently under review in DCRP. The (b) (4) proposed labeling changes to the **Boxed Warning**, **Warning and Precautions**, and **Adverse Reactions** sections (b) (4) for which DCRP has requested DMEP's input. The proposed labeling changes include:

1. Revision of the language describing the increased risk of lower limb amputations observed in the two large cardiovascular outcome trials with canagliflozin in patients with established CV disease or at risk for CV disease (CANVAS and CANVAS-R, collectively referred to as the CANVAS program) to report results in terms of incidence rates rather than relative risk
2. (b) (4)
3. Revision of the text describing the risk of renal carcinoma in CANVAS-R in Section 6

Of note, on July 11, 2018 the Applicant submitted prior approval efficacy supplement (b) (4) (b) (4) describing the increased risk of lower limb amputations (i.e., to report absolute risk rather than relative risk), and also proposed adding language (b) (4) However, the Applicant's proposal to describe the amputation data from CANVAS and CANVAS-R in the Boxed Warning (b) (4) in terms of absolute risk rather than relative risk, and to report incidence rates that were already present in the Warning and Precautions (b) (4) was deemed reasonable. Because those changes were not considered sufficiently substantive to approve new labeling, it was determined that they could be implemented during the next opportunity (b) (4)

II. Materials Reviewed

1. Draft labels for NDA 204042 S-32 (INVOKANA/canagliflozin), (b) (4)
2. Applicant's submitted rationales for removing fracture from Warnings and Precautions proposed USPI changes related to description of amputations
3. CREDENCE Clinical Overview and Clinical Study Report

III. DMEP Comments and Recommendations

1. Amputations:

Applicant's Proposed Labeling Change	DMEP Comments and Recommendation
Boxed Warning: An ~~approximately 2-fold~~ increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS -R (7.5 vs 4.2 events per 1000 patient-years), two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD	The Applicant's rationale for this proposed change was reviewed and determined to be acceptable during review of sNDA 204042 S-(b) (4) The Applicant states that "2-fold increased risk" is nonspecific and that prescribing physicians misinterpret the term due to confusion regarding the concept of relative risk. DMEP determined that presenting incidence rates, so that absolute risk can be derived easily by prescribers, is acceptable. DMEP recommends accepting this proposed labeling change.
Boxed Warning: (b) (4)	This information is not appropriate for the **Boxed Warning** section of the labeling, which should provide "a brief, concise summary of the information that is critical for a prescriber to consider, including any restriction on distribution or use" per the Boxed Warning section of labeling guidance. DMEP recommends deleting this statement from the **Boxed Warning**.
Warnings and Precautions: An ~~approximately 2-fold~~ increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years)	This proposed labeling change is acceptable from DMEP's perspective.
Warnings and Precautions: (b) (4)	Per the W&P section of labeling guidance, the description of the adverse reaction in this section should be succinct and limited to a numerical estimate of risk; known risk factors for the adverse reaction; steps taken to decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction; and how to treat or otherwise manage an adverse reaction. As such, the Applicant's proposed change is not appropriate for the W&P section of the labeling. This information (b) (4)

	(b) (4) should be removed from **Warnings and Precautions**.
Adverse Reactions: (b) (4)	DMEP recommends the following rephrasing of this description: *"The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively in CREDENCE,* (b) (4) *outcomes study of patients with type 2 diabetes and* (b) (4) *with 2.6 years mean duration of follow-up."* This description of the results presents incidence rates (b) (4) and specifies the duration of follow-up in CREDENCE. Of note, although we typically do not include negative information in **Adverse Reactions**, labeling guidance states that a negative finding can be reported if the absence of the reaction is "convincingly demonstrated in a trial of adequate design and power". The CREDENCE population was at high-risk for amputation events and collected a reasonable number of events despite the shorter-than-planned duration of the trial (70 patients had amputations in the canagliflozin arm vs. 63 in the placebo arm). Therefore it seems reasonable to include this information in Section 6 as it may be helpful information for prescribers.

2. Bone Fractures

Applicant's Proposed Labeling Change	DMEP Comments and Recommendation
Warnings and Precautions: (b) (4)	(b) (4)

	(b) (4) DMEP does not agree (b) (4) (b) (4)
Adverse Reactions: (b) (4)	DMEP recommends removing this statement from the **Adverse Reactions** section of the label. (b) (4)
Adverse Reactions: (b) (4)	DMEP recommends removing this statement from the **Adverse Reactions** section. (b) (4)
Adverse Reactions: (b) (4)	(b) (4)

	(b) (4) DMEP recommends removing this statement from the **Adverse Reactions** section of the label.

3. Renal Cell Carcinoma

Applicant's Proposed Labeling Change	DMEP Comments and Recommendation
Adverse Reactions: The Applicant has relocated the Renal Cell Carcinoma subheading of the Adverse Reactions section, which describes the imbalance in events observed in the CANVAS trial, to the end of Section 6.1, and added the following statement: (b) (4)	Labeling guidance states that the beginning of the **Adverse Reactions** section should identify the most clinically significant adverse reactions. As such, DMEP recommends retaining the original placement of the renal cell carcinoma subheading. (b) (4) DMEP recommends removing this statement.

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/s/

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PATRICK ARCHDEACON
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 20, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 204042/S-32
Product Name and Strength:	Invokana (Canagliflozin) tablets, 100 mg and 300 mg
Product Type:	Single Ingredient Product (Invokana)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Pharmaceuticals Inc. (Janssen)
FDA Received Date:	September 6, 2019
OSE RCM #:	2019-697
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

Janssen submitted an NDA efficacy supplement for Invokana (NDA 204042) to support inclusion of the new indication to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, and cardiovascular (CV) death in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day.

This review responds to the Division of Cardiovascular and Renal Products (DCRP) April 11, 2019 consult for DMEPA to evaluate the proposed Invokana Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may 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
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Invokana PI and MG submitted on March 27, 2019 and found the proposed dosing information provided in Section 2 of the PI confusing. The Division evaluated the data submitted to the NDA supplement and made significant revisions to the Dosage and Administration sections to clarify dosing. We agree with their revisions and provided a few additional edits below:

A. Invokana PI, Section 2 Dosage and Administration

    a. We recommend adding the units for eGFR measurement (e.g., mL/min/1.73 m^2) in the Table 1 column titled "Renal Considerations" and in the paragraph below Table 1, as well as the units for albuminuria measurements in Section 2.

b. We recommend adding the route of administration and the phrase "…, taken before the first meal of the day" after the recommended dosage for eGFR≥ 60 in Table 1 (e.g., 100 mg orally once daily, taken before the first meal of the day).

B. Invokana PI, Section 16 How Supplied/Storage and Handling

a. Consider expressing the storage temperature to include a temperature range per USP (e.g., Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]).

DCRP communicated our recommendations to Janssen and subsequently, Janssen submitted revised labeling on August 15, 2019 and on September 6, 2019, which incorporated our recommendations. Our review of the latest proposed PI and MG submitted September 6, 2019 did not identify any additional issues from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Invokana received on March 27, 2019 from Janssen Pharmaceuticals Inc. (Janssen).

Table 2. Relevant Product Information for Invokana	
Initial Approval Date	March 29, 2013
Active Ingredient	Canagliflozin
Indication	Currently approved: • as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD). *Proposed:* • (b) (4)
Route of Administration	oral
Dosage Form	tablets
Strength	100 mg and 300 mg
Dose and Frequency	*Proposed:* (b) (4) Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers: (b) (4)

[1] Screenshot image taken from the proposed draft labeling text submitted on March 27, 2019

	(b) (4)
How Supplied	100 mg and 300 mg tablets: bottles of 30, 90, 500 (b) (4)
Storage	(b) (4)
Container Closure	100 mg tablet: 40 mL and 75 mL HDPE bottle with (b) (4) induction seal; 160 mL HDPE bottle with continuous thread closure and induction sea (b) (4) 300 mg tablet: 40 mL, 75 mL, 160 mL HDPE bottle with (b) (4) induction seal; 750 mL HDPE bottle with continuous thread closure and induction sea (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 29, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, canagliflozin, Invokana, and NDA # 204042. Our search identified one previous, relevant labeling review with prescribing information recommendations (see below table 3 below), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3

No.	Review Citation
1.	Agustin, R. Label and Labeling Review for Invokana (NDA 204042). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 30. RCM No.: 2012-1302.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 26, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the labels and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR
Search Strategy and Terms	Match Any of the Words: Invokana

D.2 Results

The search retrieved 7 articles, but none of the articles described medication errors relevant to this labeling review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Invokana labeling submitted by Janssen Pharmaceuticals Inc. (Janssen).

- Prescribing Information (Image not shown) received on March 27, 2019, August 15, 2019, and September 6, 2019.
- Medication Guide (Image not shown) received on March 27, 2019, August 15, 2019, and September 6, 2019.

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

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

PATIENT LABELING REVIEW

Date:	September 19, 2019
To:	Norman Stockbridge, MD Director **Division of Cardiovascular and Renal Products (DCaRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	INVOKANA (canagliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204042
Supplement Number:	S-32
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On March 27, 2019, Janssen Research & Development, LLC submitted for the Agency's review an efficacy supplement to their New Drug Application (NDA) 204042/S-32 for INVOKANA (canagliflozin) tablets. This supplement proposes a new indication: (b) (4)

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 Cardiovascular and Renal Products (DCaRP) on April 11, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INVOKANA (canagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft INVOKANA (canagliflozin) tablets MG received on March 27, 2019, and received by DMPP and OPDP on September 13, 2019.
- Draft INVOKANA (canagliflozin) tablets Prescribing Information (PI) received on March 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 13, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the MG we:

- 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)

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

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

Memorandum

Date: September 16, 2019

To: Anna Park, Regulatory Project Manager, Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for INVOKANA (canagliflozin) tablets, for oral use

NDA: 204042/Supplement 032

In response to DCRP consult request dated April 11, 2019, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for Invokana. This supplement (S032) provides for a new renal indication based on the addition of the CREDENCE study to section 14.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DCRP (Anna Park) on September 13, 2019, and are provided below.

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

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

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