

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205879Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 6, 2016

To: Elizabeth Godwin, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205879
OPDP labeling comments for INVOKAMET XR (canagliflozin and metformin hydrochloride extended release) tablets, for oral use

On November 23, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and Medication Guide for INVOKAMET XR (canagliflozin and metformin hydrochloride extended release) tablets, for oral use. OPDP's comments on the proposed draft labeling are based on the version sent by Elizabeth Godwin via email on August 18, 2016, and are marked on the version provided directly below.

OPDP does not have any comments on the proposed PI at this time.

Comments on the Medication Guide are provided in a collaborative review between DMPP and OPDP under a separate cover.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
09/06/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	September 2, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 205879
Product Name and Strength:	Invokamet XR (canagliflozin and metformin extended release), tablet 50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg
Submission Date:	August 26, 2016
Applicant/Sponsor Name:	Janssen Pharmaceuticals Inc.
OSE RCM #:	2015-2543-1
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

DMEP requested that we review the revised professional sample container labels for Invokamet XR (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

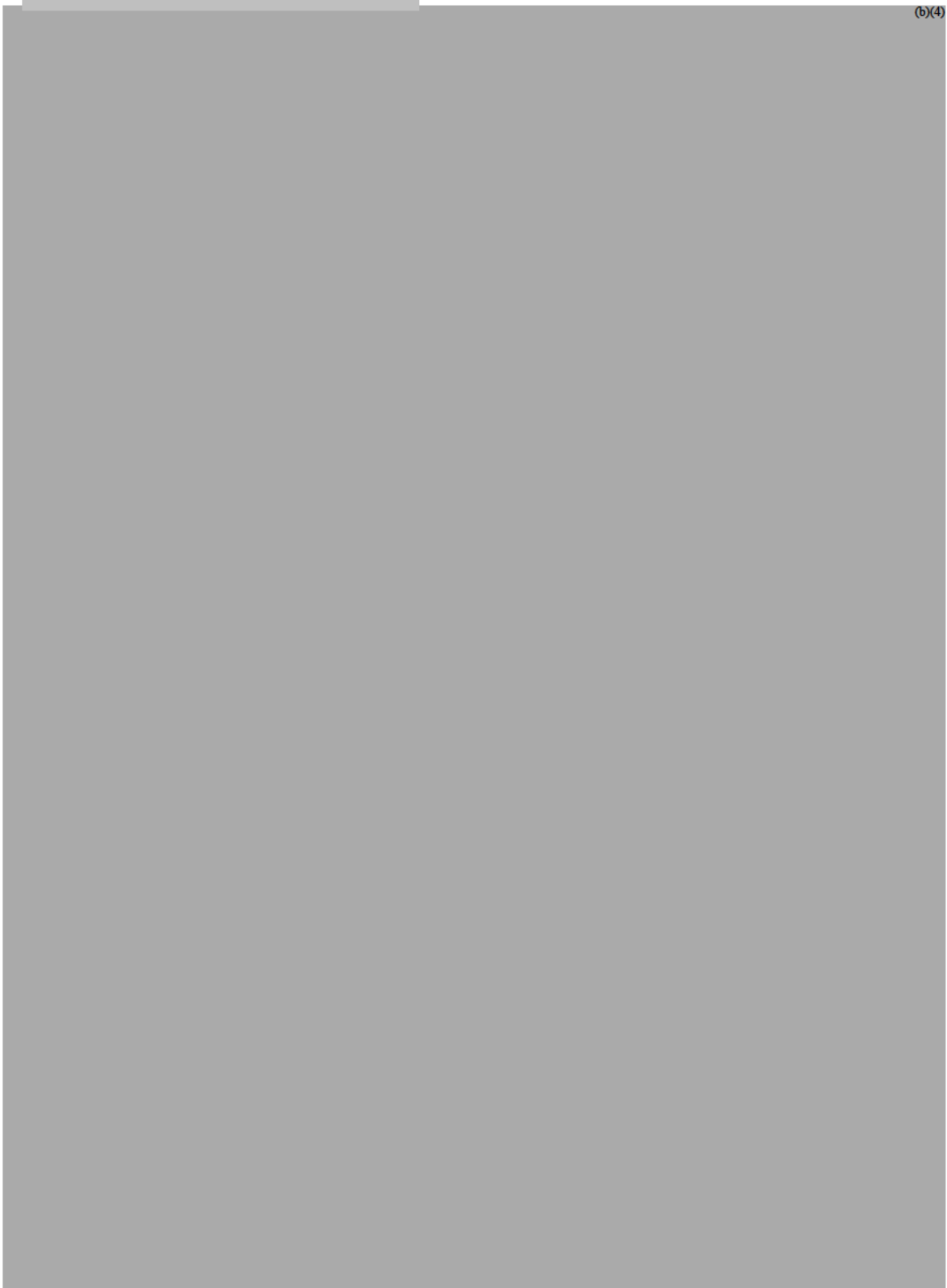
2 CONCLUSION

The revised professional sample container labels for Invokamet XR are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Conrad A. Label and Labeling Review for Invokamet XR (NDA 205879). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 4. 14 p. OSE RCM No.: 2015-2543.

APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 26, 2016

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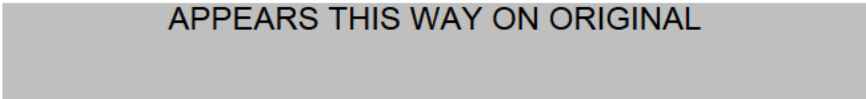


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/s/

ARIANE O CONRAD
09/02/2016

HINA S MEHTA
09/02/2016

**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 23, 2016

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
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)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 205879

Applicant: Janssen Research & Development, LLC

1 INTRODUCTION

On November 20, 2015, Janssen Research & Development submitted for the Agency's review an Original New Drug Application for INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use. INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.

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 November 23, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use MG received on November, 20, 2016, and received by DMPP and OPDP on August 18, 2016.
- Draft INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use Prescribing Information (PI) received on November 20, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 18, 2016.
- Approved INVOKAMET (canagliflozin and metformin hydrochloride) tablets comparator labeling dated May 20, 2016.

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.

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)
- 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
08/23/2016

CHARUNI P SHAH
08/23/2016

MARCIA B WILLIAMS
08/23/2016

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:	August 4, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 205879
Product Name and Strength:	Invokamet XR (canagliflozin and metformin extended release), tablet 50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg
Product Type:	Multi-ingredient product
Rx or OTC:	RX
Applicant/Sponsor Name:	Janssen Pharmaceuticals Inc.
Submission Date:	November 20, 2015 and June 10, 2016
OSE RCM #:	2015-2543
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 REASON FOR REVIEW

Janssen Pharmaceuticals submitted NDA 205879 for Invokamet XR (canagliflozin and metformin extended release) tablet on November 20, 2015. The Division of Metabolism and Endocrinology Products (DMEP) requested we evaluate the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors.

1.1 REGULATORY HISTORY

Immediate release Invokamet (canagliflozin and metformin) tablets were approved on August 8, 2014 under NDA 204353. The same Applicant has submitted this NDA for an extended release formulation of Invokamet.

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)*	B
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS for 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 performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. In addition, we reviewed the approved labels and labeling for Invokamet (NDA 204353), so that comparisons could be made with the immediate release formulation.

Our review identified a deficiency in the sample container labels. We provide recommendations in section 4.1 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Janssen increase the readability and prominence of important information in the proposed labeling to clarify information and mitigate any confusion that may interfere with the safe use of Invokamet XR.

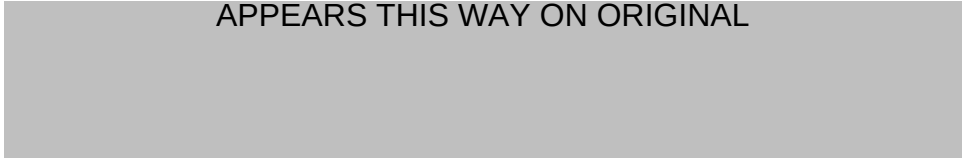
4.1 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS INC.

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

A. Professional Sample Container Labels

1. Increase the size and prominence of the “Sample-Not for Sale” statement so that it is clear that these are drug samples, per 21CFR 203.38(c).

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Invokamet XR that Janssen submitted on November 20, 2015.

Table 2. Relevant Product Information for Invokamet XR	
Initial Approval Date	N/A
Active Ingredient	canagliflozin and metformin extended release
Indication	Type 2 diabetes mellitus
Route of Administration	oral
Dosage Form	Extended-release tablet
Strength	50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg
Dose and Frequency	2 tablets once daily with the morning meals, with a gradual dose escalation to reduce the gastrointestinal side effects due to metformin
How Supplied	Bottle of 60 tablets
Storage	Store at 68-77 F (20-25 C). Store in the original container.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 2, 2016 using the criteria below, and then individually reviewed each case.

Table 3. FAERS Search Strategy to Identify Medication Error Cases for Invokamet	
Date Range	August 8, 2014 to July 31, 2016
Product	canagliflozin and metformin [product active ingredient] Invokamet [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
Country (Derived)	USA

B.2 Results

Our search of FAERS identified 89 U.S. suspected medication error cases of which 25 are not relevant for this review. The cases are summarized below.

Table 4. Summary of U.S. Suspected Invokamet Medication Error Cases in FAERS, August 8, 2014 to July 31, 2016		
Type of Medication Error or Event	# of U.S. Cases	DMEPA Reviewer Comment
Improper Storage	2	• Improper storage of Invokamet in pill box (n=2)
Incorrect drug administration	15	• Patient inappropriately splitting or crushing tablets (n=5) • Patient lowered dose from twice daily to once

Table 4. Summary of U.S. Suspected Invokamet Medication Error Cases in FAERS, August 8, 2014 to July 31, 2016		
Type of Medication Error or Event	# of U.S. Cases	DMEPA Reviewer Comment
		daily (n=6) • Patient administration of expired Invokamet (n=3) • Patient switched from Invokana to Invokamet in error but etiology unclear based on information provided in report (n=1)
Dispensing error	6	• Two different tablet strengths were dispensed in the same pharmacy bottle (n=2) • Medication was dispensed in a pharmacy bottle instead of the original container (n=2) • Invokana and Invokamet dispensed in the same pharmacy bottle (n=1) • Number of tablets dispensed fewer than prescribed (n=1)
Possible prescribing error	41	• Dose prescribed once daily instead of twice daily (n=28) • Both Invokana and Invokamet prescribed (n=5) • More than 2 tablets prescribed per day (n=4) • Prescription written for the wrong tablet strength or a non-existent tablet strength (n=2) • One-half then one-quarter tablet prescribed daily (n=1) • Prescribed for a patient with diabetes mellitus type 1 (n=1)
Other	25	• Described events not related to a medication error with Invokamet (n=16) • Described errors for Invokana (canagliflozin) instead of Invokamet (n=5) • Error type unclear based on information provided in report (n=4)

Invokamet (canagliflozin and metformin) is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and the approved dose is 1 tablet administered twice daily. Off-label dose adjustments (i.e., once daily instead of twice daily dosing) were the most frequent medication errors reported. These adjustments may have been made to offset the known GI tolerability issues with the metformin component of the product; however, the product labeling does not include this dose schedule as an option.

We reviewed the prescribing information and container label for Invokamet and it appears that the information in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information (PI) is clearly presented. In addition, the label and PI contain statements specifying the storage requirements for this product. Thus, we do not recommend revisions to the Invokamet labeling at this time and we do not have recommendations for the Invokamet XR labeling based on the errors identified with Invokamet.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

	<u>FAERS Case ID</u>	<u>Version</u>	<u>Manufacturer Control Number</u>
1.	10972016	2	US-JNJFOC-20150317916
2.	11111971	2	
3.	11192318	2	US-JNJFOC-20150605785
4.	11391108	2	US-JNJFOC-20150807669
5.	11398785	2	US-JNJFOC-20150808880
6.	11816715	2	US-JNJFOC-20151100163
7.	10940688	2	US-JNJFOC-20150106969
8.	10940696	2	US-JNJFOC-20150205403
9.	10940698	4	US-JNJFOC-20150110727
10.	10940732	2	US-JNJFOC-20150304992
11.	10942260	2	US-JNJFOC-20141011231
12.	10942264	2	US-JNJFOC-20141016869
13.	11056437	2	US-JNJFOC-20150304968
14.	11056442	2	US-JNJFOC-20150305009
15.	11056451	2	US-JNJFOC-20150321368
16.	11056462	1	US-JNJFOC-20150405794
17.	11056464	1	US-JNJFOC-20150407179
18.	11057055	1	US-JNJFOC-20150400531
19.	11188155	1	US-JNJFOC-20150503807
20.	11188156	1	US-JNJFOC-20150503799

	<u>FAERS Case ID</u>	<u>Version</u>	<u>Manufacturer Control Number</u>
21.	11188199	1	US-JNJFOC-20150515672
22.	11188211	1	US-JNJFOC-20150508138
23.	11263828	1	US-JNJFOC-20150621801
24.	11369603	1	US-JNJFOC-20150503720
25.	11369663	1	US-JNJFOC-20150720948
26.	11369924	1	US-JNJFOC-20150503684
27.	11369925	1	US-JNJFOC-20150503633
28.	11369926	1	US-JNJFOC-20150503650
29.	11369928	1	US-JNJFOC-20150503588
30.	11369958	1	US-JNJFOC-20150705030
31.	11369962	1	US-JNJFOC-20150705026
32.	11369983	1	US-JNJFOC-20150718747
33.	11369990	1	US-JNJFOC-20150802271
34.	11369992	1	US-JNJFOC-20150802288
35.	11369994	1	US-JNJFOC-20150803848
36.	11369997	1	US-JNJFOC-20150715755
37.	11370095	1	US-JNJFOC-20150710246
38.	11459410	1	US-JNJFOC-20150815847
39.	11612964	1	US-JNJFOC-20150904032
40.	11613033	1	US-JNJFOC-20150924353
41.	11736106	1	US-JNJFOC-20151002213
42.	11736176	1	US-JNJFOC-20151006767
43.	11816747	1	US-JNJFOC-20151102432
44.	11884251	1	US-JNJFOC-20151212020
45.	11884320	1	US-JNJFOC-20151207756
46.	11056618	1	US-JNJFOC-20150405764
47.	11133800	1	US-JNJFOC-20150304956
48.	11370052	1	US-JNJFOC-20150503750

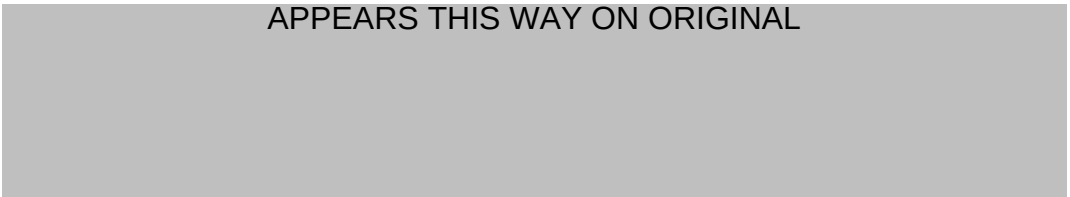
	<u>FAERS Case ID</u>	<u>Version</u>	<u>Manufacturer Control Number</u>
49.	11370115	2	US-JNJFOC-20150720946
50.	12107810	1	US-JNJFOC-20151225415
51.	12107814	2	US-JNJFOC-20160116588
52.	12107820	1	US-JNJFOC-20160206672
53.	12198072	1	US-JNJFOC-20160312737
54.	12236650	1	US-JNJFOC-20160324787
55.	12462865	1	US-JNJFOC-20160506861
56.	12462866	1	US-JNJFOC-20160510271
57.	12462868	2	US-JNJFOC-20160515468
58.	12171441	2	US-JNJFOC-20160304995
59.	12525299	1	US-JNJFOC-20160627958
60.	12287189	1	US-JNJFOC-20160416373
61.	12462906	2	US-JNJFOC-20160527544
62.	12524661	2	US-JNJFOC-20160627975
63.	12236643	1	US-JNJFOC-20160314601
64.	12462870	2	US-JNJFOC-20160509183

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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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,¹ along with postmarket medication error data, we reviewed the following Invokamet XR labels and labeling submitted by Janssen on November 20, 2015.

- Container labels
- Professional Sample Container Labels
- Medication Guide

C.2 Label and Labeling Images

Container Labels



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

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/s/

ARIANE O CONRAD
08/04/2016

HINA S MEHTA
08/04/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Division of Pediatric and Maternal Health Memorandum

Date: May 9, 2016 **Date consulted:** December 16, 2015

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

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

To: Division of Metabolic and Endocrine Products (DMEP)

Drugs: Invokamet [canagliflozin and metformin fixed dose combination (FDC)]
and Invokamet XR [canagliflozin and metformin hydrochloride extended release
Fixed Dose Combination (Cana/Met XR FDC)]

NDA: 204353/ S-006, an Efficacy Supplement with data
205879, a new NDA

Applicant: Janssen Research & Development, LLC, Pharmaceutical Companies of Johnson-
Johnson

Class: A combination product of a sodium-glucose co-transporter 2 (SGLT2) inhibitor
and metformin, a biguanide

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of Type 2 Diabetes Mellitus

Materials Reviewed:

- DPMH consult requests dated December 16, 2015 in DARRTS.

- Applicant's submitted background package for the sNDA: 204353/006 dated July 20, 2015 and new NDA 205879 dated November 20, 2015.
- Applicant's response to information request (IR) by the Division on October 14, 2015, dated December 1, 2015.

Consult Question:

DMEP requests that DPMH determine if the PLLR formats in the proposed Prescribing Information (PIs) are acceptable.

REGULATORY HISTORY

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 16, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Invokamet [canagliflozin and metformin hydrochloride fixed dose combination (FDC)] and Invokamet XR [canagliflozin and metformin hydrochloride extended release Fixed Dose Combination (CANA/MET XR FDC)] to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

The purpose of the supplemental NDA (sNDA) 204353/ S-006 is to provide clinical data from a recently completed Phase 3 study. Data from this study may support the use of Invokamet as an initial therapy in patients with Type2 Diabetes Mellitus (T2DM). The proposed change in the indication statement is as follows:

Current Indication: Invokamet (canagliflozin and metformin hydrochloride) is indicated as an 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, or in patients who are already treated with both canagliflozin and metformin (Invokamet United States Prescribing Information (USPI), August 2014).

Proposed Indication: Invokamet (canagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.
NDA 205879 is a new NDA.

DPMH will review in tandem both NDAs in this review.

To further support the proposed labeling in PLLR format, DMEP sent Janssen an information request on October 14, 2015 requesting:

- A review and summary of all available published literature regarding Invokamet and its components related to drug use in pregnant and lactating women
- A review and summary of relevant cases from the Applicant's pharmacovigilance database
- A revised labeling incorporating the above information that complies with PLLR format to support changes to the Pregnancy and Lactation sections of labeling.

In addition to other changes to the labeling, Janssen responded by proposing revisions to the Pregnancy and Lactation sections of the labeling per FDA Draft Guidance Pregnancy,

BACKGROUND

Diabetes Mellitus and Pregnancy

Adverse outcomes of diabetes during pregnancy relate to the onset of diabetes, its duration, and the degree of vasculopathy. Women with pregnancies complicated by diabetes mellitus may be separated into one of two groups:

1. Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy. This means that the glucose intolerance may have antedated the pregnancy but was not recognized by the patient or the physician.
2. Pregestational diabetes (PGD): women known to have diabetes before pregnancy.

Ninety percent of all pregnant diabetic women have gestational diabetes mellitus (GDM), whereas type 1 (insulin-dependent diabetes) and type 2 (non-insulin dependent diabetes) account for the remaining 10%¹.

Gestational Diabetes

The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the United States. The likelihood of developing GDM is significantly increased among certain subgroups. These include women with a family history of type 2 diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of major congenital malformations (MCM) has passed. PGD that is well under control is not associated with an increased risk either, however, infants of women with poorly controlled PGD have an increased risk of MCM.²

Pregestational Diabetes

Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. Fetal complications include pyelonephritis, hypertensive disorders and macrosomia-related injuries (brachial plexus injury, hypoxia). Also directly related to metabolic control are fetal hyperglycemia and neonatal hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

¹ Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008

² Mastroyannis, C. Lixisenatide labeling review in DARRTS, April, 2016

Infants of diabetic mothers in unsatisfactory glycemic control often develop hypoglycemia during the first few hours of life. The reported incidence ranges from 25% to 40% of infants of diabetic mothers. Poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of hypoglycemia in the infant. Clinical studies suggest that euglycemia during organogenesis in pregestational pregnant diabetics is critical in the prevention of congenital anomalies.¹ Poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HemoglobinA1c>7 and has been reported to be as high as 20-25% in women with a Hemoglobin A1c>10. In addition, poorly controlled DM may result in fetal complications, including macrosomia-related injuries (brachial plexus injury, hypoxia), fetal hypoglycemia, and respiratory distress.³ Achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.^{4,5,6}

Poorly controlled pre-gestational diabetes mellitus (PGD) (before conception and in the first trimester) is associated with Major Congenital Malformation (MCM) (5-10%) and spontaneous abortion (15-20%).⁷ The higher the fasting serum glucose level is at diagnosis, the higher the incidence of MCM.⁸ The Micromedex database states that pregestational diabetes mellitus in pregnant women with poor control during organogenesis is associated with a 3-fold increase in congenital anomalies that include cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Offspring of mothers with poorly controlled PGD during pregnancy have a mortality rate that is 5 times greater than that of non-diabetic mothers; the mortality rate is higher at all gestational ages.⁹

The American College of Obstetricians and Gynecologists (ACOG) in a statement issued in 2005 and reaffirmed in 2012 for PGD, states that HbA_{1c} of 5-6% is associated with a fetal malformation rate close to what is seen in normal pregnancies. A HbA_{1c} near 10% is associated with a fetal anomaly rate of 20-25%.¹⁰

Invokamet Drug Characteristics

Invokamet tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: canagliflozin and metformin hydrochloride¹¹

³ Dinatale, M: Labeling review consult, in DARRTS, May 2016

⁴ Mills JL. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94

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

⁶ www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.

⁷ Ornoy, et al. Effect of Maternal Diabetes on the Embryo, Fetus, and Children: Congenital Anomalies, Genetic and Epigenetic Changes and Developmental Outcomes. *Birth Defects Research, Part C: Embryo Today: Reviews*. 2015; 105(1): 53-72.

⁸ Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165-1171.

⁹ The Behrman RE, Kleigman RM, Nelson WE, et al: *Nelson Textbook of Pediatrics*, 14th. WB Saunders Company, Philadelphia, PA, 1992.

¹⁰ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

Invokamet XR Drug Characteristics¹²

Invokamet XR is an oral fixed dose combination tablet of canagliflozin for immediate release and metformin hydrochloride for extended release. Each bilayer tablet is compressed from two separate granulates, one for each active ingredient of the tablet, and finished with a film-coating. The metformin HCl extended release layer is based on a polymer matrix which controls the drug release by passive diffusion through the swollen matrix in combination with tablet erosion.

Excipients

The inactive ingredients in Invokamet XR different from Invokamet include: hydroxypropyl cellulose, lactose anhydrous, polyethylene oxide, and silicified microcrystalline cellulose (50 mg/500 mg and 50 mg/1,000 mg tablets only). The tablets are finished with a commercially available film-coating consisting of the following inactive ingredients: macrogol/PEG3350, iron oxide red, iron oxide yellow, and iron oxide black (50 mg/1,000 mg and 150 mg/1,000 mg tablets only).

Canagliflozin Drug Characteristics¹³

Canagliflozin is an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, canagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. Half-life of canagliflozin was estimated to be between 10.6 hours and 13.1 hours. Steady state can be reached after 4 to 5 days of once-daily dosing. Serious adverse events that have occurred with use of canagliflozin include ketoacidosis, serious urinary tract infections (pyelonephritis), hypoglycemia, genital mycotic infections, hypersensitivity reactions, bone fractures, hyperlipidemia (LDL-C), hypotension, hyperkalemia and impairment in renal function.

Metformin Drug Characteristics^{14,15}

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes by lowering basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin has a molecular weight of 165.65 Daltons, a plasma elimination half-life of six hours, and does not bind to proteins. Serious adverse events that have occurred with use of metformin include: lactic acidosis and impairment of renal function. Metformin does not induce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

¹¹ Invokamet existing labeling, Sections 5 (Warnings and Precautions) and 12 (Clinical Pharmacology)

¹² Invokamet XR proposed labeling, dated November 20, 2015

¹³ Invokana (canagliflozin) existing labeling

¹⁴ Dinatale, M., Mastroyannis, C. Labeling review for Actos products, in DARRTS, March and April, 2016

¹⁵ Dinatale, M. Labeling review for Jentadueto XR, May 2016

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁶ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

The Applicant performed a literature search and assessment related to the co-administration of canagliflozin and metformin in pregnant and lactating women, and females and males of reproductive potential, as well as when each canagliflozin and metformin are used as monotherapy. The Applicant has conducted literature searches of the clinical and nonclinical published literature as well as conducted a search of its own pharmacovigilance database for any new and relevant cases not previously identified or reviewed for the USPIs in order to conform to the PLLR.

Nonclinical Experience

Mutagenesis

Canagliflozin

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the in vitro mouse lymphoma assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an in vivo oral micronucleus assay in rats and an in vivo oral Comet assay in rats.¹³

Metformin

There was no evidence of mutagenic potential for metformin in the following in vitro tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.^{14,15}

Canagliflozin monotherapy and Canagliflozin + Metformin (Invokamet) (free dose or fixed dose combination):

Non-clinical data

Pregnancy

All data in regards to pregnancy has previously been reported and reviewed by the FDA. The reader is referred to the Pharmacology/Toxicology Review by F. Alavi, Ph.D. in DARRTS. No adverse developmental effects were observed when canagliflozin and metformin were co-

¹⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹⁷ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

administered to pregnant rats during the period of organogenesis at exposures up to 11 and 13 times, respectively, the 300mg and 2000mg the maximum recommended human doses (MRHD) of canagliflozin and metformin based on AUC, as per Pharmacology/Toxicology Review.

Canagliflozin

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was 0.5-times the 300mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period. Similar effects on the developing kidney were not seen when canagliflozin was administered to pregnant rats or rabbits during the period of organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, wherein pups were indirectly exposed in utero and throughout lactation.

In embryo fetal development studies, no developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100mg/kg in pregnant rats and 160mg/kg in pregnant rabbits during embryonic organogenesis, yielding exposures up to approximately 19-times the 300mg clinical dose, based on AUC.

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2 and 6-times a 2000 mg clinical dose based on body surface area (mg/m²) for rats and rabbits, respectively. The reader is referred to the full Pharmacology/Toxicology review by T. Bourcier, Ph.D. and D. Carlson, Ph.D. for further details.

Lactation

Canagliflozin

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Data from a study in juvenile rats who were directly administered canagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. See Invokamet labeling, Section 8.3-Nursing Mothers, approved on March 28, 2016.

Metformin

Studies in lactating rats show that metformin is present in the milk and reaches levels comparable to those in plasma. See Invokamet labeling, Section 8.3-Nursing Mothers, approved on March 28, 2016

Fertility

Invokamet

No animal studies have been conducted with the combination of canagliflozin and metformin to evaluate any effects on fertility.

Canagliflozin

There were no adverse effects of treatment on male or female fertility in rats in spite of reductions in some sperm endpoints at 15 times the human dose. Female rats had a small decrease in number of corpora lutea and fewer implantation sites at 18 times the human dose. There were no histologic alterations in the reproductive organs of treated dogs.¹³ Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons

LITERATURE REVIEW and GLOBAL MEDICAL SAFETY DATABASE (PHARMACOVIGILANCE) SEARCH

The Applicant searched the Medline, Derwent, EMBASE, and Biosis (OVID Platform) databases covering a period up to October 2015. DPMH also conducted a review of PubMed, ReproTox, and TERIS for published literature regarding canagliflozin plus metformin, Invokamet, Vokanamet, sodium glucose co-transporter-2 (SGLT-2) inhibitors, dapagliflozin and related drug terms: pregnancy, teratogenicity, and birth defects. In addition to the applicant's search of published literature for information about metformin use during pregnancy and lactation, DPMH also conducted a literature search in PubMed, Embase, ReproTox, and TERIS. The results of the literature search are described below.

The Applicant's Global Medical Safety (GMS) database was also searched for cumulative reported cases with canagliflozin/metformin FDC through September 28, 2015, that are relevant to pregnancy, lactation, and reproductive potential. A search was also done for reported cases with canagliflozin monotherapy with concomitant metformin through September 28, 2015. Search for the words canagliflozin/metformin, or canagliflozin was performed for cases of all reporting sources (spontaneous, literature, clinical trials), medically or non-medically confirmed. The Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) was searched for neonate or infant and congenital, familial and genetic disorders or pregnancy, puerperium and perinatal conditions and for breast feeding.

Human Data

Pregnancy

Canagliflozin

There is no human data available on canagliflozin monotherapy and canagliflozin + metformin (free dose or fixed dose combination) use in pregnant women (clinical trials or epidemiologic studies). The drug is not recommended for use in the second or third trimester of pregnancy or during lactation. This recommendation is based on renal tubule and pelvis dilatation after direct treatment of juvenile rats.^{13,14,18} TERIS states that the magnitude of teratogenic hazard to a child

born after exposure during gestation is undetermined because there is no data on which risk may be based. There are no human studies on canagliflozin use in pregnant women. All women who take canagliflozin during pregnancy have diabetes, which itself can adversely affect embryonic and fetal development.

Metformin¹⁹

Metformin is primarily used in women with pre-gestational diabetes and used off label in women with polycystic ovary syndrome (PCOS) for infertility. For treatment of pre-gestational diabetes, metformin is often continued during pregnancy and insulin is added as appropriate to the therapy regimen. In women with polycystic ovary syndrome, metformin is often continued until the end of the first trimester, with only limited evidence to suggest that such use decreases the risks of adverse pregnancy outcomes, including first-trimester loss.²⁰ Metformin use in women with gestational diabetes has not been approved by the U.S. Food and Drug Administration. Women with diabetes treated with metformin during the 1st trimester of pregnancy showed no increase in congenital defects over untreated women with diabetes.²¹ A study of 171 women exposed to metformin during the first trimester of pregnancy showed no increase in the rate of birth defects among their infants.²² Another study compared the incidence of anomalies in 475 type 2 diabetic women, 82 treated with oral hypoglycemic agents (metformin or glyburide), 239 treated with diet alone, and 154 who received insulin. Diabetic treatment prior to pregnancy and during the first 9 weeks of pregnancy was evaluated. No increase in the incidence of anomalies was found in any group.^{23,24}

The Metformin in Gestational Diabetes (MiG) trial was a large (n=751) randomized, open label trial comparing the use of metformin versus insulin in the treatment of gestational diabetes. The primary focus of the study was on neonatal outcomes. There was no significant difference in the primary composite outcome (neonatal hypoglycemia, respiratory distress, phototherapy need, birth trauma, 5 minute APGAR score <7 and prematurity) between the two arms (32% metformin vs 32.2% insulin [p=0.95], RR=0.99, 95% CI 0.8-1.23). There were more incidences of neonatal severe hypoglycemia (blood glucose levels <28.8mg/dL) with insulin compared to metformin (8.1% vs 3.3%, p=0.008). There was a significant increase in the number of preterm births (<37 weeks gestation) with metformin compared to insulin (12.1% vs 7.6%, p=0.04).

¹⁸ Kelley K.W., Carroll D.G., Meyer A. A review of current treatment strategies for gestational diabetes mellitus. *Drugs in Context.* 2015;4 Article Number 212282

¹⁹ Dinatale, M. and Mastroyannis, C. MHT review of Actos combination products, DARRTS; March, 2016 and addendum of April, 2016

²⁰ De Leo V, Musacchio MC, Piomboni P, Di Sabatino A, Morgante G. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. *Eur J Obstet Gynecol Reprod Biol* 2011;157:63–6.

²¹ Coetzee, E.J. and Jackson, W.P.U.: Oral hypoglycemics in the first trimester and fetal outcome. *S. Afr. Med. J.* 65:635-637, 1984

²² Diav-Citrin, O.; Steinmetz-Shoob, S.; Shechtman, S. and Ornoy, A.: Pregnancy outcome following in utero exposure to metformin: A prospective comparative observational study. *Birth Defects Res. A Clin. Mol. Teratol.* 100(7):520, 2014

²³ Langer O, Conway D, Berkus M, Xenakis EM: There is no association between oral hypoglycemic use and fetal anomalies. *Am J Obstet Gynecol* 1999;180:S38

²⁴ Carrol, D., Kelley, K.: Review of metformin and glyburide in the management of gestational diabetes. *Pharm Pract (Granada).* 2014 Oct-Dec; 12(4): 528

However, there was minimal clinical difference in mean gestational age between the two agents (38.3 weeks with metformin versus 38.5 weeks with insulin).²⁵

Since the MiG trial, nine other metformin studies (randomized control trials, case-control trials and observational studies) in women with gestational diabetes have been published. Six trials compared metformin to insulin^{26,27,28,29,30,31} and three trials compared metformin to glyburide.^{32,33,34} For all but one of the studies that compared insulin to metformin [24, 25, 26, 27, 29], there were no differences in birth weight, gestational age, mode of delivery, prematurity or perinatal deaths. One trial [28] reported more infants with birth weights >90th percentile (35% versus 17.5%, $p=0.012$) and higher birth weights (3.4 kg versus 3.3kg, $p\text{-value}=0.005$) in the insulin group compared to the metformin group. For trials that compared metformin to glyburide, there was no difference in maternal blood glucose, neonatal hypoglycemia, macrosomia or gestational age of delivery. Other studies have also demonstrated that there is no increased risk of birth defects or adverse perinatal outcomes (decreased fetal growth, neonatal hypoglycemia) in infants exposed to metformin in utero.^{35,36,37,38}

There is one study, by Panchaud, A. et. al., that demonstrated an increased rate of birth defects, spontaneous abortions, and preterm birth in metformin-exposed pregnancies. In a multicenter, prospective cohort study, 323 pregnant women with pre-gestational diabetes exposed to metformin were compared to a matched control group of patients not exposed to teratogenic agents or to any other anti-diabetic medications. Major congenital anomalies were more frequent

²⁵ Rowan, J. et al. Metformin versus Insulin for the Treatment of Gestational Diabetes. *The New England Journal of Medicine*. 2008; 358: 2003-2015.

²⁶ Tertti, et al. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective case-control study. *Rev Diabet Stu*. 2008; 5 (2): 95-101.

²⁷ Balani, et al. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. *Diabet Med*. 2009; 26 (8):798-802.

²⁸ Ijäs, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG*. 2011; 118(7):880-885.

²⁹ Niromanesh, et al. Metformin compared with insulin in the management of gestational diabetes: a randomized clinical trial. *Diabetes Res Clin Pract*. 2012;98(3):422-9.

³⁰ Tertti K, et al. Metformin vs insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab*. 2013;15(3):246-251.

³¹ Spaulonci, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol*. 2013; 209(1):34.e1-7.

³² Silva, et al. Metformin compared to glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet*. 2010;111(1):37-40.

³³ Moore, et al. Metformin compared with glyburide in gestational diabetes. *Obstet Gynecol*. 2010;115(1):55-59

³⁴ Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. *J Perinat Med*. 2012;40(3):225-228.

³⁵ Bolton S, Cleary B, Walsh J, Dempsey E, Turner MJ. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. *Eur J Pediatr*. 2009; 168(2):203-206

³⁶ Gilbert C, Valois M, Koren G. Pregnancy outcomes after first trimester exposure to metformin: a meta-analysis. *Fertil Steril*. 2006 Sep;86(3):658-663

³⁷ Briggs GG, editor. 9th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. Metformin. *Drugs in Pregnancy and Lactation*; pp. 912-915

³⁸ Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstet Gynecol* 2009; 113:193-205. (Meta-analysis)

among the infants of 323 women who had used metformin during pregnancy than among control infants (7.6% vs. 2.5% respectively; odds ratio=3.2, 95% confidence interval 1.3-9.2, p=0.005).³⁹ The authors noted that there is a potential for confounding effects of the underlying metabolic disease and that further data collection and analysis of potential bias was being undertaken at the time the results of the study were published.

Reviewer comment:

In the study by Panchaud, A. et al., the metformin-exposed population was made up of patients with pre-gestational diabetes and the control population was made up of non-diabetic patients. This reviewer agrees with the authors that a patient who has an existing diabetes diagnosis is at higher risk of congenital malformations, and it is likely that increased rate of congenital malformations seen in the metformin-exposed pregnancies was due to the underlying diabetes and not necessarily due to metformin use during pregnancy.

The American College of Obstetrics and Gynecology (ACOG) recently updated its position statement regarding the use of oral medications in the treatment of gestational diabetes and noted that both glyburide and metformin have favorable safety profiles.⁴⁰

Metformin Use in PCOS and Type 2 Diabetes Mellitus

Data from PCOS and Type 2 Diabetes Mellitus (i.e., DM that was present prior to pregnancy) studies may provide information on the effects of metformin use in the first trimester of pregnancy. In published observational studies that have reviewed metformin use during the first trimester of pregnancy, there have been no reports of an association with metformin use in the first trimester of pregnancy and the risk of major birth defects, miscarriage or adverse perinatal outcomes (decreased fetal growth, neonatal hypoglycemia) in infants.^{41,42,43,44,45,46} There are two studies that have demonstrated an increase in complications with metformin use during pregnancy. In a retrospective cohort study (Hellmuth, et al.) to assess maternal and neonatal complications in pregnancies of diabetic women treated with oral hypoglycemic agents, 50 pregnant women treated with metformin were compared to 68 women treated with sulfonylurea. The control group included 42 women treated with insulin during pregnancy. The authors found that the prevalence of pre-eclampsia was increased in the metformin group

³⁹ Panchaud, A., Baud, D., Vial T. et al. Pregnancy outcome following maternal exposure to metformin: Preliminary results of a collaborative ENTIS and Motherisk study. *Birth Defects Res. A Clin. Mol. Teratol.* 100(7):521, 2014

⁴⁰ Practice Bulletin No. 137: Gestational diabetes mellitus. Committee on Practice Bulletins--Obstetrics. *Obstet Gynecol.* 2013 Aug;122(2 Pt 1):406-16

⁴¹ Bolton, et al. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. *Eur J Pediatr.* 2009;168(2):203-206

⁴² Gilbert C, Valois M, Koren G. Pregnancy outcomes after first trimester exposure to metformin: a meta-analysis. *Fertil Steril.* 2006 Sep;86(3):658-663

⁴³ Briggs GG, editor. 9th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. Metformin. *Drugs in Pregnancy and Lactation*; pp. 912-915

⁴⁴ Diav-Citrin, O.; Steinmetz-Shoob, S.; Shechtman, S. and Ornoy, A.: Pregnancy outcome following in utero exposure to metformin: A prospective comparative observational study. *Birth Defects Res. A Clin. Mol. Teratol.* 100(7):520, 2014

⁴⁵ Glueck CJ, et al. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod.* 2002 Nov;17(11):2858-64.

⁴⁶ Coetzee, E.J. and Jackson, W.P.U.: Oral hypoglycemics in the first trimester and fetal outcome. *S. Afr. Med. J.* 65:635-637, 1984

compared to the sulfonylurea and insulin groups (32% versus 7% versus 10%, p-value <0.001). There was also an increase in perinatal mortality in the metformin group versus women not treated with metformin (11.6% versus 1.3%, p-value <0.02).⁴⁷

Reviewer comments:

In the study reviewed above, the women in the three cohorts had similar characteristics except that the women in the metformin group were more likely to be obese (pre-pregnancy BMI was 31.2 compared to 22.8 and 24.8 in the sulfonylurea and insulin groups). An obese or overweight patient with type 2 diabetes is at an increased risk of preeclampsia, cesarean delivery, shoulder dystocia, preterm delivery, large-for-gestational age infant, fetal malformations and admission of the infant into the neonatal intensive care unit. Therefore, it is difficult to determine whether the increased prevalence of pre-eclampsia was due to metformin use or due to obesity.^{48, 49}

Summary

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

Review of Pharmacovigilance on Pregnancy⁵⁰

Three cases were identified from clinical trials.

1. A 21-year-old woman with no previous medical history (gravida 0, para 0) had a negative serum pregnancy test on Day -1 of each treatment period (ie, Period 1 and Period 2). At the end-of-study follow-up visit (approximately 9 days after receiving the single dose of reference study therapy in Period 2), her serum pregnancy test was positive. The subject reported that she experienced a spontaneous abortion approximately 2 months later and she underwent a dilation and curettage. There are no additional records. The adverse event of spontaneous abortion was judged by the investigator as not related to study drug because of the timing (2 months after the last dose of the drug).
2. A 33-year-old Hispanic woman from the United States became pregnant while treated with canagliflozin 100 mg twice daily, orally for 3 months and also taking concomitant metformin for diabetes mellitus type 2. On Day 86 at the routine Week 12 visit (end-of-study visit), the subject had a positive urine pregnancy test. She was treated with ongoing, subcutaneous insulin injections (started on Day 100). The subject's last menstrual period was 20 days before the subject received her first dose of study drug. Patient gave birth to a normal baby girl by cesarean section at 38 weeks gestation.
3. A 39-year-old Mexican woman was receiving canagliflozin study therapy (300 mg/day) for 4 months with metformin therapy (2,550 mg/day). She was suspected to be pregnant and a urine pregnancy test was positive. Treatment with the study drug was discontinued on Day 113

⁴⁷ Hellmuth, et al. Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabetic Medicine*. 2000; 17: 507-511

⁴⁸ www.cdc.gov. Reproductive Health: Maternal and Infant Health and Pregnancy Complications. Accessed 12/18/2015.

⁴⁹ Racusin, et al. Obesity and the Risk and Detection of Fetal Malformations. *Seminars in Perinatology*. 2012; 36(3): 213-221.

⁵⁰ Applicant's response to information request (IR) by the Division on September October 14, 2015, dated December 1, 2015

due to the event of high risk pregnancy and all concomitant medications, including metformin, were stopped. The patient continued treatment only with insulin. She had an uneventful pregnancy. C-section was performed at 37 weeks gestation. She delivered a normal newborn who was breastfed.

There is one spontaneous post-marketing report

1. A 37-year-old Hispanic/Latino female patient from the United States was treated with canagliflozin 300 mg once daily, orally for an unspecified duration of time for treatment of diabetes mellitus type 2. Concomitant medications included metformin for type 2 diabetes. The patient reported that she unexpectedly got pregnant and canagliflozin was discontinued on an unspecified date in September 2014. The patient's last menstrual period and expected delivery date were both unspecified. The patient delivered a healthy normal newborn.

Pregnancy Exposure Registry

There is no pregnancy exposure registry established that monitors pregnancy outcomes in women exposed to canagliflozin/metformin during pregnancy.

Lactation

The results of the literature search by the Applicant and DPMH for terms like lactation, breastfeeding and breast milk in humans are described below.

Human Data

Invokamet/canagliflozin

No clinical studies have been conducted with the combined components of the drug product regarding the presence of Invokamet in human milk, the effects on the breastfed infant, or the effects on milk production. Therefore, there is no information about Invokamet and lactation.

In Hale's Medication and Mother's Milk, there are no entries on Invokamet or canagliflozin.⁵¹ No records also exist about Invokamet or canagliflozin in LactMed.⁵² LactMed recommends that an alternate drug is preferred, especially while nursing a newborn or preterm infant because no information is available on the use of canagliflozin during breastfeeding. Since human kidney maturation occurs in utero and during the first 2 years of life when Lactational exposure may occur, there may be risk to the developing human kidney.

Metformin

The applicant performed a literature search in Medline and Embase to identify published literature on lactation-related publications for metformin. In addition to the applicant's search of published literature for information about metformin use during lactation, DPMH also performed a search of the Drugs and Lactation Database (LactMed) and PubMed and Embase.

⁵¹ Hale, T. Medications and Mother's Milk. Hale Publishing, 2012

⁵² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding

In a lactation study (Eyal, et al.), breast milk samples were collected from four women with either PCOS or diabetes (Type 2 diabetes mellitus or gestational diabetes) who were treated with metformin (1500 mg/day in one patient; 2000 mg/day in three patients) in the post-partum period. The amounts of metformin detected in breast milk daily were 0.13, 0.15, 0.21 and 0.28 mg with corresponding relative infant doses of 0.21, 0.14, 0.21 and 0.43% of the mother's weight adjusted dose, respectively. Maternal and infant serum samples were not collected, and there was no information about any effects of metformin on the infant.⁵³

See the previous DPMH review⁵⁴ by Miriam Dinatale, D.O. and Christos Mastroyannis for a complete review of other lactation studies^{55,56,57,58,59,60,61} that were performed in women taking metformin.

In a lactation study (Hale, et al.), seven women (ages 26- 38 years) who took metformin orally (median dose of 1500 mg daily) and their infants (5-25 months old) were studied. The mean milk-to-plasma ratio was 0.35 (range: 0.13 to 0.58). The mean relative infant dose was 0.28% (range: 0.15 to 0.42%) of the maternal weight-adjusted dosage. Based on maternal (n=4) and/or physician (n=2) observation, the infants appeared to be developing normally. In two infants, a Denver Developmental Screening test was done, which was normal. The developmental outcome for one infant was unknown.^{62,63}

Another published article (Gardiner, et al.), reported on two lactation studies. In one lactation study, two lactating women (14 and 14.5 months post-partum) took a single dose of immediate-release metformin. In a second lactation study, five healthy lactating women (in the process of weaning), were given metformin 500mg, and studied for 72 hours. The milk-to-plasma ratio ranged between 0.27 and 0.5, and the relative infant dose ranged between 0.11% and 0.25% for both studies.⁶⁴

⁵³ Eyal S, Easterling TR, Carr D, et al. Pharmacokinetics of metformin during pregnancy. *Drug Metabolism & Disposition*. 2010 May; 38(5):833-40

⁵⁴ DPMH review of pioglitazone products. March 9, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3898973.

⁵⁵ Hale TW, et al. Transfer of metformin into human milk. *Diabetologia*. 2002; 45:1509-14.

⁵⁶ Hale T, et al. Transfer of metformin into human milk. *Adv Exp Med Biol*. 2004; 554:435-6.

⁵⁷ Gardiner SJ, Kirkpatrick CM, Begg EJ et al. Transfer of metformin into human milk. *Clin Pharmacol Ther*. 2003;73:71-7

⁵⁸ Briggs GG, Ambrose PJ, Nageotte MP et al. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol*. 2005;105:1437-41.

⁵⁹ Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr*. 2006;148:628-32.e2

⁶⁰ Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril*. 2006;85:1002-9

⁶¹ Vanky E, Nordskar J, Leithe H et al. Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo. *BJOG*. 2012;119:1403-9

⁶² Hale TW, Kristensen JH, Hackett LP et al. Transfer of metformin into human milk. *Diabetologia*. 2002;45:1509-14

⁶³ Hale T, Kristensen J, Hackett L et al. Transfer of metformin into human milk. *Adv Exp Med Biol*. 2004;554:435-6

⁶⁴ Gardiner SJ, Kirkpatrick CM, Begg EJ et al. Transfer of metformin into human milk. *Clin Pharmacol Ther*. 2003;73:71-7

In a lactation study (Briggs, et al.), seven women were started on metformin 500mg twice daily right after their cesarean section. Two women were excluded from the study, and two other women stopped breastfeeding but continued to provide breast milk samples. Serum and milk samples were collected from the mothers on postpartum days 4 and 17. Three infants had blood glucose levels drawn at the same time as maternal samples. The mean milk/serum ratio was 0.63 (range 0.36 to 1), and the relative infant dose was 0.65% (range 0.43 to 1.08%). In three infants, the blood glucose concentration after four hours of feeding was normal (47 to 77mg/dL). The mothers reported no side effects in the infants.⁶⁵

The breastfed infants of mothers, who were taking metformin during lactation, developed normally and experienced no adverse effects. None of the infants studied had low blood glucose levels and their mothers reported no adverse reactions in the infants. Metformin had no effect on duration of breastfeeding.^{66,67}

Summary

There is no information about Invokamet or canagliflozin and lactation. Metformin is present in breast milk in low levels. In a review of published literature of metformin use during lactation, the milk-to-plasma ratio ranged between 0.13 to 1, and the relative infant dose ranged between 0.11 to 1%. A drug that has a milk-to-plasma ratio that is less than one is considered safe to use while breastfeeding.⁶⁸ A drug with a relative infant dose of less than 10% of the maternal dose, is considered safe for use during breastfeeding. Metformin did not appear to have any adverse effects on two breastfed infants that were evaluated by physicians in the lactation study by Hale, et al. However, there is limited information on the effect of metformin on a breastfed infant. LactMed notes that data from clinical lactation studies demonstrate that metformin levels in breast milk are low. Metformin should be used with caution when women are breastfeeding neonates and premature infants, especially those with renal impairment.

*Review of Pharmacovigilance on Lactation*⁵⁰

No cases of breastfeeding were identified either from clinical trials or post-marketing data.

Current Invokamet labeling recommends that because of the potential for serious adverse reactions in nursing infants from Invokamet, [human kidney maturation occurs in utero and during the first 2 years of life when Lactational exposure may occur, there may be risk to the developing human kidney by canagliflozin (see non-clinical review of canagliflozin and lactation above)]. Therefore, a decision should be made whether to discontinue nursing or to discontinue Invokamet, taking into account the importance of the drug to the mother. DPMH recommends that use of Invokamet is not recommended while breast feeding because of the potential for serious adverse reactions to the infant.

⁶⁵ Briggs GG, Ambrose PJ, Nageotte MP et al. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol.* 2005;105:1437-41.

⁶⁶ Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr.* 2006;148:628-32.e2

⁶⁷ Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril.* 2006;85:1002-9

⁶⁸ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. *Journal of the American Pharmacists Association.* 2012; 51 (1): 86-94.

Females and Males of Reproductive Potential

The Applicant performed a literature review of Medline, Embase and PubMed for terms like reproduction potential, fertility, infertility and impairment of fertility to identify reports of reproductive toxicity with Invokamet use in humans. No reports were identified. In addition to the search of published literature performed by the applicant, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of Invokamet and canagliflozin and their effects on fertility. No additional data were identified. No cases of impaired fertility in women or men exposed to canagliflozin and metformin combination or canagliflozin monotherapy with concomitant metformin were identified in the published literature.

Metformin

In addition to the search of published literature performed by the applicant, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of metformin and its' effects on fertility. Metformin is used off-label for the treatment of PCOS and has been shown to increase ovulation and the potential for pregnancy in women taking the drug.^{69,70} There is no evidence of infertility in patients who take metformin. Therapy with metformin can lead to ovulation in some premenopausal anovulatory women and may result to unintended pregnancy while taking Invokamet.

Reviewer comment

Metformin may increase ovulation and the potential for unintended pregnancy. Women who are taking metformin-containing products should be informed of the possibility of unintended pregnancy. Therefore, Section 8.3, Females and Males of Reproductive Potential, should note that metformin may result in ovulation in premenopausal anovulatory women and increase the potential for unintended pregnancy.

Review of Pharmacovigilance on Females and Males of Reproductive Potential⁵⁰

The applicant has conducted a review of the pharmacovigilance database, as well as the published literature for cases of impaired fertility associated with the use of canagliflozin and metformin combination or canagliflozin monotherapy with concomitant metformin, and the results are summarized below.

Clinical Trials Data

No cases were identified in clinical trials of impaired fertility in women or men exposed to canagliflozin and metformin combination or canagliflozin monotherapy with concomitant metformin.

Postmarketing Data

No spontaneous reports were found in the postmarketing database of impaired fertility in women or men exposed to canagliflozin and metformin combination or canagliflozin monotherapy with concomitant metformin.

CONCLUSIONS

⁶⁹ Polycystic Ovarian Syndrome Medication. www.medscape.com. Accessed 12/31/2015.

⁷⁰ Sangeeta, S. Metformin and Pioglitazone in Polycystic Ovarian Syndrome: A Comparative Study. 2012; 62(5): 551-556.

Invokamet labeling has been updated to comply with the PLLR. DPMH has the following recommendations for Invokamet labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of Invokamet labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” subsections⁷¹.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of Invokamet labeling was formatted in the PLLR format to include: “Risk Summary” and “Data.”⁷²
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” subsection of Invokamet labeling was formatted in the PLLR format. Since there is no evidence of infertility in animal studies or in humans, (b) (4)
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of Invokamet labeling was updated to correspond with changes made to sections 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

DPMH has participated in meetings with DMEP regarding metformin combination products during the months of March and April 2016. DPMH revised sections 8.1, 8.2, 8.3 and 17 of Invokamet labeling for compliance with the PLLR (see below). DPMH refers to the NDA action for final labeling.

⁷¹ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

⁷² Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

⁷³ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed Invokamet Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- Lactation: INVOKAMET is not recommended when breastfeeding. (8. 2)
- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data based on post-marketing reports with INVOKAMET or its components in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see *Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

In animal studies, adverse renal effects that were not reversible were observed when canagliflozin was administered to juvenile rats during a period that corresponds to the late second and third trimesters of human renal development at exposure 0.5-times the 300mg clinical dose, based on AUC [see *Data*]. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

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

because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Canagliflozin and Metformin

No adverse developmental effects were observed when canagliflozin and metformin were co-administered to pregnant rats during the period of organogenesis at exposures up to 11 and 13 times, respectively, the 300mg and 2000mg clinical doses of canagliflozin and metformin based on AUC.

Canagliflozin

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period. Similar effects on the developing kidney were not seen when canagliflozin was administered to pregnant rats or rabbits during the period of organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, wherein pups were indirectly exposed in utero and throughout lactation.

In embryo fetal development studies, no developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100mg/kg in pregnant rats and 160mg/kg in pregnant rabbits during embryonic organogenesis, yielding exposures up to approximately 19-times the 300mg clinical dose, based on AUC.

Metformin Hydrochloride

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKAMET or canagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [see Data]. However, canagliflozin is present in rat milk. Limited published studies report that metformin is present in human milk. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Canagliflozin is present in the milk of lactating rats [see Data]. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKAMET is not recommended while breastfeeding

Data

Human Data

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

Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKAMET is not recommended while breastfeeding.

Animal Data

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.3 Females and Males of Reproductive Potential

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

17 PATIENT COUNSELING INFORMATION

- **Pregnancy:** Advise pregnant women and females of reproductive potential of the potential risk to a fetus with treatment with INVOKAMET [see use in Specific Populations (8.1)]. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.
- **Lactation:** Advise women that breastfeeding is not recommended during treatment with INVOKAMET [see *Use in Specific Populations* (8.2)].
- Inform females that treatment with INVOKAMET may result in ovulation in some premenopausal anovulatory women, which may lead to unintended pregnancy [see *Use in Specific Populations* (8.3)].

MEDICATION GUIDE

- **are pregnant or plan to become pregnant.** INVOKAMET may harm your unborn baby. If you become pregnant while taking INVOKAMET, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- **are a premenopausal woman (before the “change of life”), who does not have periods regularly or at all.** INVOKAMET may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking INVOKAMET, if you are not planning to become pregnant. Tell your doctor right away if you become pregnant while taking INVOKAMET.
- **are breastfeeding or plan to breastfeed.** INVOKAMET may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking INVOKAMET. Do not breastfeed while taking INVOKAMET.

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

/s/

CHRISTOS MASTROYANNIS

05/13/2016

TAMARA N JOHNSON

05/13/2016

LYNNE P YAO

05/15/2016

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

DATE: 3/8/2016

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 205879

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Sites inspection

Facility Type	Facility Name	Facility Address
Clinical	Celerion, Inc.	2420 West Baseline Road, Tempe, AZ
Analytical	(b) (4)	

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

/s/

SHILA S NKAH
03/08/2016

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 # 205879	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Invokamet XR (pending) Established/Proper Name: canagliflozin and metformin hydrochloride extended release Dosage Form: tablets Strengths: 50/500, 150/500, 50/1000 and 150/1000 mg		
Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 11.20.2015 Date of Receipt: 11.20.2015 Date clock started after UN:		
PDUFA Goal Date: 9.20.2016		Action Goal Date (if different):
Filing Date: 1.19.2016		Date of Filing Meeting: 1.11.2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both canagliflozin and metformin is appropriate		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 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 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: <i>The application will be a priority review if:</i> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 110533				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA 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>	☒	☐		
Are the 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</i>	☒	☐		

to the supporting IND(s) if not already entered into tracking system.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
User Fee Status <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>		Payment for this application (check daily email from UserFeeAR@fda.hhs.gov): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<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>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
User Fee Bundling Policy <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (Check the 356h form,		☐	☒		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		☐	☐		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☐		
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity 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>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/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>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐		
If yes, # years requested: 3 years					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>		☒		
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☐	

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

1

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

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☐	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <u>paper</u> forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <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?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>	☒	☐		

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

<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	IND 110533 12.19.2014
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> 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>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	Submitted 12.9.2015
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

2

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

3

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

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ 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>				
Is the PI submitted in PLR format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☒	☐	Only canagliflozin information included
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☐			
Check all types of labeling submitted.	☒ Not Applicable			
	☐ Outer carton label			

4

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

5

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

	☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
Is electronic content of labeling (COL) submitted?	YES	NO	NA	Comment: Yes
<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?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	☐	☐	☐	
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	YES	NO	NA	Comment: No additional consults needed
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	☐	☐	☐	
End-of Phase 2 meeting(s)? Date(s):	YES	NO	NA	Comment: No EOP2 Meeting
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Pre-NDA meeting held on June 25, 2014 Pre-NDA CMC meeting WRO Nov. 25, 2013		☐		Pre-NDA and Pre-NDA CMC meetings were held
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)?	☐	☒		

Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				
	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 11, 2016

BACKGROUND:

This new NDA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate. Submission cross-refers to NDA 204042 (approved March 29, 2013) for the primary safety and efficacy data supporting the canagliflozin portion of the application, and NDA 021748, Glumetza (approved June 3, 2005) for the safety and efficacy of metformin XR.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Abolade (Bola) Adeolu	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Lisa Yanoff		Y
Division Director/Deputy	Jean-Marc Guettier		N
Office Director/Deputy			
Clinical	Reviewer:	Hyon Kwon	Y
	TL:	Lisa Yanoff	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Renu Singh	Y
	TL:	Manoj Khurana	Y

• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Roberto Crackel	Y
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fred Alavi	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Martin Haber	N
• Drug Product	Reviewer:	Elise Luong	N
• Process	Reviewer:	Shujun Chen	N
• Microbiology	Reviewer:	Shujun Chen	N
• Facility	Reviewer:	Mike Klapal	N
• Biopharmaceutics	Reviewer:	Hansong Chen	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (EA Reviewer)	James Laurensen		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Marcia Britt-Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Shah Charuni	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ariane Conrad	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline MHT *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Christos Mastroyannis	Y
	TL:	Tamara Johnson	Y
Other attendees	Christian Hampp		Y
	Terrolyn Thomas		Y
	Ali Niak		Y
	Christine Chamberlain		Y
	Julie Van der Waag		Y
	Patricia Bright		Y
	Tanjinatus Oishi		Y
	Ariane Conrad		Y
	Anika Lalmansingh		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
--	--	--

Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☒ Not Applicable ☐ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <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>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	N/A ☐ YES ☐ NO ☒ YES ☐ NO

<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) - Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? - If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
What late submission components, if any, arrived after 30 days?	
Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO
--	---

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jean-Marc Guettier, MD, Division Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: September 2014

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
01/20/2016

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

Application: NDA 205879

Application Type: New NDA

Drug Name(s)/Dosage Form(s): canagliflozin and metformin HCl extended release tablets

Applicant: Janssen Pharmaceuticals Inc.

Receipt Date: November 20, 2015

Goal Date: September 20, 2016

1. Regulatory History and Applicant's Main Proposals

This new NDA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate. Submission cross-refers to NDA 204042 (approved March 29, 2013) for the primary safety and efficacy data supporting the canagliflozin portion of the application, and NDA 021748, Glumetza (approved June 3, 2005) for the safety and efficacy of metformin XR.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the

Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[*see Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 35. All text in the BW should be **bolded**.

Comment:

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- NO** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Applicant states: “.....it is not generally not possible to reliably.....”*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABOLADE ADEOLU
01/20/2016