



NDA 204353/S-025  
NDA 205879/S-007

**SUPPLEMENT APPROVAL**

Janssen Pharmaceuticals, Inc.  
Attention: Brandon D. Porter  
Associate Director, Global Regulatory Affairs  
920 U.S. Highway 202, P.O. Box 300  
Raritan, NJ 08869-0602

Dear Mr. Porter:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received September 29, 2017, and your amendments, submitted pursuant to section 505(b)(2) and under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokamet (canagliflozin and metformin hydrochloride) tablets and Invokamet XR (canagliflozin and metformin hydrochloride extended release) tablets.

We acknowledge receipt of your major amendments dated June 28, 2018, which extended the goal date by three months.

These Prior Approval supplemental new drug applications provide for a new indication “Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD). However, the effectiveness of INVOKAMET/INVOKAMET XR on reducing the risk of major cardiovascular events in adults with type 2 diabetes and cardiovascular disease has not been established” for Invokamet and Invokamet XR based on the results of the studies 28431754DIA3008, entitled, “A Randomized, Multicenter, Double- Blind, Parallel, Placebo- Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus,” (CANVAS) and 28431754DIA4003, entitled, “A Randomized, Multicenter, Double-Blind, Parallel, Placebo- Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus,” (CANVAS-R).

**APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

The pagination has been revised so that the Medication Guide's page numbers begin with page number 1.

### **WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for these applications because necessary studies are impossible or highly impracticable. This was determined because atherosclerosis complications of diabetes mellitus require years to develop, and they are very rare in pediatric

patients with diabetes mellitus. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus AND high cardiovascular risk. The number of pediatric patients fitting these criteria is small, and the required length of follow-up would likely result in patients exceeding the pediatric age range. A clinical trial for the new proposed indication is therefore not feasible.

### **SENTINEL/ARIA NOTIFICATION**

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate canagliflozin in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: renal cell carcinoma.

The ARIA safety assessment will be posted to the Sentinel website at this location: <https://www.sentinelinitiative.org>. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Liz Godwin, Regulatory Project Manager, at 240-402-3438.

Sincerely,

*{See appended electronic signature page}*

Lisa Yanoff, MD  
Deputy Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### ENCLOSURES:

Content of Labeling  
Prescribing Information  
Medication Guide

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

LISA B YANOFF  
10/29/2018