DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204353/S-003

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Brandon Porter
Associate Director, Global Regulatory Affairs
3210 Merryfield Row
San Diego, CA 92121

Dear Mr. Porter:

Please refer to your Supplemental New Drug Application (sNDA) dated September 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokamet (canagliflozin and metformin HCl) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We acknowledge receipt of your amendments dated November 21, 2014, and March 16, 2015. We also acknowledge receipt of your agreed-upon labeling by e-mail on August 14, 2015.

This "Prior Approval" supplemental new drug application provides for the following major changes to the package insert:

Under Section 5 **WARNINGS AND PRECAUTIONS**, added the following sub-section:

5.9 Bone Fracture
An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin. Consider factors that contribute to fracture risk prior to initiating INVOKAMET *[see Adverse Reactions (6.1)]*.

Under Section 6 **ADVERSE REACTIONS**, sub-section 6.1 **Clinical Studies Experience**, added the following sections:

Falls
In a pool of nine clinical trials with mean duration of exposure to canagliflozin of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The higher risk of falls for patients treated with canagliflozin was observed within the first few weeks of treatment.

Bone Fracture
The occurrence of bone fractures was evaluated in a pool of nine clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities *[see Warnings and Precautions (5.9)]*.

Under the heading, Laboratory *and Imaging* Tests:

Increases in Serum Potassium
In a pooled population of patients (N=723) with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with canagliflozin 100 mg, and 1.3% of patients treated with canagliflozin 300 mg.
In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions (5.3), (5.4) and Use in Specific Populations (8.6)]*.

Decreases in Bone Mineral Density
Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years). At 2 years, patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both canagliflozin doses and 0.4% at the distal forearm for patients randomized to canagliflozin 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to canagliflozin 100 mg was 0%.

Under Section 8 **USE IN SPECIFIC POPULATIONS**, sub-section 8.6 **Renal Impairment**, edited the following paragraphs:

The efficacy and safety of canagliflozin were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2). Dose-related, transient mean increases in serum potassium were observed early after initiation of canagliflozin

(i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2), (5.3), (5.4), and Adverse Reactions (6.1)]*.

The efficacy and safety of canagliflozin have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. Canagliflozin is not expected to be effective in these patient populations *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

This supplemental new drug application also provides for a change to the Medication Guide, as well as minor editorial changes to the package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revision listed below and reflected in the enclosed labeling:

- Revision date changed to "09/2015" to reflect the date of approval for this supplement.

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 package insert 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 includes labeling changes for this NDA, 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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 package insert(s) 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 package insert(s), 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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).

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 Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling
Package Insert
Medication Guide

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

/s/

JEAN-MARC P GUETTIER
09/10/2015