

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204353Orig1s000

Trade Name: Invokamet Tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

Generic Name: canagliflozin and metformin hydrochloride

Sponsor: **Janssen Pharmaceuticals, Inc.**

Approval Date: August 8, 2014

Indications: 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 already being treated with both canagliflozin and metformin.

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APPROVAL LETTER



NDA 204353

NDA APPROVAL

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

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) dated December 12, 2012, received December 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg.

We acknowledge receipt of your amendments dated January 18, February 11, March 12, April 9, 26, and 30, May 3, June 27 and 28, August 13 and 15, September 18, October 14, November 6 and 14, 2013, and January 3(2), and 21, February 10 and 13, March 11 and 13, May 29, June 11 and 17, July 1 and 7, and August 4, 2014. We also acknowledge receipt of your email dated August 8, 2014, which includes the agreed-upon labeling.

The February 10, 2014, submission constituted a complete response to our December 11, 2013, action letter.

This new drug application provides for the use of Invokamet (canagliflozin and metformin hydrochloride) tablets 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 already being treated with both canagliflozin and metformin.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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). Information on submitting SPL files using eLIST may be found in the guidance for industry SPL Standard for Content of Labeling Technical Qs and As, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on May 29, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204353.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Invokamet (canagliflozin and metformin hydrochloride) tablets, 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg was not referred to an FDA advisory committee because this drug is not the first in its class and the safety profile is similar to that of other drugs acceptable for the treatment of type 2 diabetes. Also, outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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.

We are waiving the pediatric study requirement for ages 0 through 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2761-1 A study to evaluate whether pediatric patients with type 2 diabetes ages 10 to 17 years (inclusive) or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Invokamet tablets. The study should evaluate tablets that are the same dimensions as the largest Invokamet tablet, and placebo tablets should be used if the study population consists of healthy subjects.

Final Protocol Submission: May 2015
Study Completion: May 2017
Final Report Submission: November 2017

Submit the protocol to your IND 110545, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We also remind you that your requirements under PREA as stated in the approval letter for NDA 204042 for Invokana (canagliflozin) tablets, dated March 29, 2013, also apply to NDA 204353:

2027-1 A clinical pharmacology study to evaluate the pharmacokinetics, pharmacodynamics, and safety of canagliflozin in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus on metformin monotherapy.

Final Protocol Submission: October 2013
Study Completion: December 2014
Final Report Submission: June 2015

2027-2 A 26-week, randomized double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin and as monotherapy.

Final Protocol Submission: December 2015
Study Completion: June 2020
Final Report Submission: December 2020

Please cross-reference this NDA when you submit your final reports for requirements 2072-1 and 2027-2 to NDA 204042.

EXPIRY DATING PERIOD

A 24 month expiry dating period is granted for Invokamet (canagliflozin and metformin hydrochloride) tablets when stored at 20-25 °C (68-77 °F) with excursions permitted from 15 to 30 °C (59-86 °F).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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 Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

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

Enclosures:

Package Insert
Medication Guide
Carton and Container Labels

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
08/08/2014