CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205879Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	15 Sept 2016
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205879
Applicant	Janssen Research and Development, LLC
Date of Submission	20 Nov 2015
PDUFA Goal Date	20 Sept 2016
Proprietary Name / Established (USAN) names	Invokamet XR / canagliflozin/metformin hydrochloride
Dosage forms / Strength	Oral tablets with the following dosage strengths: Canagliflozin 50 mg/metformin 500 mg extended release Canagliflozin 50 mg/ metformin 1000 mg extended release Canagliflozin 150 mg/metformin 500 mg extended release Canagliflozin 150 mg/metformin 1000 mg extended release
Proposed Indication(s)	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
Recommended:	Approval

Cross Discipline Team Leader Review

1. Introduction

Invokamet XR is a proposed fixed combination drug product (FCDP) tablet that contains two anti-diabetic medications: canagliflozin and metformin (extended release formulation). This document contains the summary review for New Drug Application 205879, submitted under the 505(b)(1) regulatory pathway for marketing approval of Invokamet XR 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. The reader is referred to the multiple discipline reviews for a more detailed discussion of the issues.

This memo references the following documents:

Subject	Author	Date
Clinical Efficacy and Safety review	Dr. Hyon Kwon	12 Sep 2016
Nonclinical review	Dr. Fred Alavi	31 May 2016
Office of Clinical Pharmacology (OCP) review	Dr. Renu Singh	16 Aug 2016
Product Quality (OPQ) review	Multiple (Dr. Suong Tran technical lead)	17Aug 2016
Statistical review (DBII)	Drs. Roberto Crackel	12 Aug 2016
Division of Pediatric and Maternal Health review (DPMH)	Dr. Christos Mastroyannis	15 May 2016
Division of Medication Error Prevention and Analysis (DMEPA) labeling review	Dr. Ariane Conrad	4 Aug 2016 2 Sep 2016
Proprietary Name review	Dr. Todd Bridges	25 Jan 2016
Office of Prescription Drug Promotion (OPDP) labeling review	Dr. Charuni Shah	6 Sep 2016
OPDP and Division of Medical Policy Programs (DMPP) Patient Labeling review	Charuni Shah and Sharon Williams	23 Aug 2016

2. Background

Canagliflozin is an orally active, competitive, reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM. It was approved for the treatment of T2DM in the US on March 29, 2013 (NDA 204402). The Sponsor of the canagliflozin NDA is Janssen Research and Development, LLC (Janssen).

Metformin is an oral biguanide, which decreases production of hepatic glucose, intestinal glucose absorption and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage (NDA 020357) on 3 Mar 1995. Metformin extended release was approved as Glucophage XR on 13 Oct 2000. Metformin extended release is also approved under the tradename Glumetza (NDA 021748) with approval date 3 Jun 2005. For the current NDA, the sponsor Janssen has a right of reference to the Glumetza NDA allowing for the 505(b)(1) regulatory pathway.

Canagliflozin in combination with metformin immediate release was approved under the tradename Invokamet (NDA 204353) on August 8, 2014 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. An Efficacy Supplement was subsequently approved (20 May 2016) to allow for an expanded indication a new indication '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.'

In sum, the majority of the data required to support approval of this NDA are derived from the following three NDAs:

NDA NUMBER	DR**UG NAME and SPONSOR**
21748	Glumetza (metformin HCl) Authorized reference from applicant (Salix)
204042	Invokana (canagliflozin) Same applicant (Janssen)
204353	Invokamet (canagliflozin/metformin HCl) Same applicant (Janssen)

The pivotal clinical studies submitted to support approval of this NDA include Clinical Pharmacology studies intended to demonstrate bioequivalence (BE) of canagliflozin/metformin extended release FDCP to co-administration of canagliflozin and metformin hydrochloride (HCl). The applicant submitted six pivotal biopharmaceutical studies conducted in healthy volunteer subjects to determine BE of cana/met XR tablets compared to the individual components under fed conditions (standardized high fat meal), and to characterize the effects of food intake on the pharmacokinetics (PK) of canagliflozin and metformin after administration of the cana/met XR tablet. The data package required to

support this NDA was agreed upon at a pre-NDA meeting 25 Jun 2014. See also Dr. Kwon's review for a detailed summary of presubmission regulatory activity related to this NDA.

3. CMC

The review from the Office of Pharmaceutical Quality (OPQ) recommends approval of this NDA. This section very briefly summarizes the findings of the overall OPQ review.

Drug Substance/Drug Product:
Canagliflozin is an inhibitor of sodium glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are C24H25FO5S•1/2 H2O and 453.53, respectively. Metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride, with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63.

NDA 204042 Invokana (canagliflozin) tablets is referenced for all CMC information on the drug substance canagliflozin. The NDA is currently approved and the reference is adequate. DMF [redacted] (b)(4) is referenced for all CMC information on the drug substance metformin HCl. The DMF is currently adequate.

The drug product is a bilayer film-coated tablet consisting of immediate release canagliflozin and extended release metformin HCl, with four strengths: 50/500, 150/500, 50/1000, 150/1000 mg/mg canagliflozin/metformin hydrochloride. The proposed FCDP is dosed two tablets once daily. The cana/met XR tablet formulations are designed as bilayer tablets with the immediate-release layer containing canagliflozin and an XR layer containing metformin HCl. The metformin HCl XR layer is a polymer matrix that controls drug release by passive diffusion through a swollen matrix in combination with tablet erosion.

The to-be-marketed FCDP tablet proposed by the applicant contains metformin HCl granulate manufactured at two sources (Janssen Ortho LLC, Gurabo [redacted] (b)(4) *Note*: The commercial manufacturing process was used to produce the bioequivalence (BE) and stability batches with 500 mg and 1000 mg metformin HCl granulates at Janssen Ortho and batches with 500 mg metformin HCl granulate [redacted] (b)(4) The manufacturing process of the 1000 mg metformin HCl granulate [redacted] (b) (4) was optimized after the production of BE batches, with adequate comparability demonstration by dissolution data and stability data (one drug product batch of each strength made with the commercial [redacted] (b)(4) 1000 mg metformin HCl granulate).

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form.

Container Closure:
HDPE bottles with desiccant [redacted] (b) (4)

Expiration Date & Storage Conditions:
24 months at room temperature. Adequate stability data are provided to support the drug substance manufacturing process.

Environmental Assessment:
A finding of no significant impact (FONSI) was recommended.

Biopharmaceutics:
All four dosage strengths, with the commercial formulations, were used in pivotal BE studies (no biowaiver request). The in vitro alcohol dose-dumping study found no dose-dumping issue. Adequate data have been provided in support of the final dissolution test method and acceptance criteria.

Manufacturing inspection was acceptable.

4. Nonclinical Pharmacology/Toxicology

This submission does not contain any new pharmacology/toxicology data. Dr. Alavi recommends approval of this NDA based on the previous finding of safety for both canagliflozin and metformin which are applicable to the application for the extended release formulation. Please see his review for details.

The potential interaction between the canagliflozin and metformin was addressed with a 3-month rat combination toxicology and a rat embryofetal development study submitted to NDA 204042 (canagliflozin) and reviewed for NDA 204353 (Invokamet). The addition of 300 mg/kg metformin to canagliflozin (cana/met doses: 4/300, 20/300 and 100/300 mg/kg/day), had no impact on the toxicological profile of canagliflozin in rats. Metformin had no impact on canagliflozin exposure; however, canagliflozin increased metformin AUC exposure by as much as 1.8 fold in rats. Since metformin is primarily excreted by renal filtration, the increase in metformin AUC is likely due to canagliflozin's effect on renal hemodynamics in rats.

In the embryofetal development study, the addition of metformin did not alter the canagliflozin associated decrease in maternal body weight and fetal skeletal variations such as reduced or incomplete ossification. The transient variations in fetal skeletal ossification were also seen with metformin alone but at lower incidence and unlikely to be clinically meaningful.

Dr. Alavi also noted that the inactive ingredients in the extended release formulation do not change the applicability of the toxicology studies conducted for each component and combination (canagliflozin + metformin).

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer Dr. Renu Singh (from the Office of Clinical Pharmacology [OCP]) recommends approval of this NDA.

As agreed upon at the preNDA meeting, the applicant provided the following Clinical Pharmacology studies to bridge to results from the canagliflozin Phase 3 program (that examined QD dosing of 100 mg and 300 mg) to support the cana/met XR tablet for the proposed indication:

- Four Phase 1 studies intended to demonstrate the BE of the to-be-marketed cana/met XR tablets to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg (Studies DIA1041, DIA1063, DIA1062, and DIA1044, respectively). A relative bioavailability study (DIA1033) served as a pilot for the 4 Phase 1 BE studies.
- A Phase 1 food effect study (DIA1064) which evaluated the effect of food on canagliflozin bioavailability following single-dose administration of the 150/1000 mg cana/met XR tablet.
- A Phase 1 multiple-dose pharmacokinetic study (DIA1042) which evaluated the multiple dose pharmacokinetics of 2 cana/met XR tablets (150 mg/1000 mg each) followed by QD oral doses.

This section briefly summarizes the findings of the OCP reviewer.

Assay Validation: The assays for analysis of canagliflozin and metformin in plasma were based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The assay was validated according to the US FDA guidance (US FDA Bioanalytical Method Validation, 2001) and all acceptance criteria as specified in those guidelines were met. All plasma PK samples from clinical studies with cana/met XR were analyzed using this validated method.

Pivotal BE studies: Cana/met XR tablets made from both manufacturing sources (see CMC section of this review) were tested for BE. All BE studies were open-label, randomized, single-center, single-dose, 3-treatment, 3-period crossover studies conducted in healthy subjects under fed conditions (standardized high fat dinner). The 90% confidence intervals for pivotal PK parameters (e.g. Cmax, AUClast and AUCinf) were contained within the pre- specified BE limits of 80% to 125% for all comparisons, and therefore, the cana/met XR tablets were demonstrated to be bioequivalent with respect to equal doses of the individual components of canagliflozin and metformin HCl XR using the to-be-marketed cana/met XR tablet strengths of 50 mg/500 mg, 150 mg /500 mg, 50 mg/1000 mg, and 150 mg/1000 mg.

Food effect: Study DIA1064 was designed to evaluate the effect of high fat meal on the oral bioavailability of canagliflozin and metformin following administration of the 150/1000 mg cana/met XR tablet. This was an open-label, randomized, single-center, and single-dose, 2-period crossover study conducted in 24 healthy subjects (16 men and 8 women).
Canagliflozin: food did not have a clinically meaningful effect on canagliflozin bioavailability and this result is consistent with previously conducted food effect studies for canagliflozin single-agent tablet.
Metformin: The median tmax for the metformin component of the cana/met XR tablet was prolonged in the fed (6 hours) vs fasted state (4 hours), indicating a slower rate of absorption in the presence of food. Additionally, Cmax was approximately 13% higher and AUClast and

AUCinf were increased by approximately 72% and 61%, respectively in the presence of food. The XR technology used for the metformin XR component of the cana/met XR tablet is the same as that used in Glumetza 500 mg tablets. This magnitude of food effect on metformin exposures for the cana/met XR tablet is consistent with that observed for Glumetza. According to approved labeling, Glumetza is recommended to be administered once daily with the evening meal, canagliflozin is recommended to be administered with the first meal of the day and Invokamet is recommended to be taken twice daily with meals. While the BE studies were conducted with evening meals the sponsor was advised at the preNDA meeting that the cana/met XR tablets should be dosed with the morning meal rather than the evening meal to avoid the potential for nighttime falls or accidents related to nocturia and hypotension, particularly in susceptible patient populations at higher risk for volume depletion (i.e., age ≥75 years, renal impairment, or on loop diuretics). The OCP reviewer concluded that the available food effect data support dosing cana/met XR with a meal and that the first meal of the day is acceptable.

Multiple-dose PK study: Study DIA1042 was conducted to assess the multiple-dose PK of canagliflozin and metformin XR following once daily administration of 2 x 150/1000 mg cana/met XR tablets in healthy subjects. This was an open-label, multiple-dose, single-center, PK study conducted in 12 healthy adult men and women for 7 days under fed conditions (standardized high fat meal). Observed accumulations in exposure parameters were expected based on the established PK of canagliflozin and metformin. Steady-state was attained by the 6th and 3rd doses for canagliflozin and metformin XR, respectively. This study suggested that there was no evidence of dose dumping with cana/met XR after multiple daily administration over 7 days. Note that this study complements the in vitro dissolution testing/alcohol interaction study.

Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for one of the pivotal BE study DIA1044 (the other pivotal studies used the same bioanalytical and clinical site). OSIS recommended accepting data without an on-site inspection because the listed sites were recently inspected by OSIS (see review by Shila S Nkah dated 03/08/2016 in DARRTS).

6. Clinical Microbiology

Not applicable to this NDA

7. Clinical/Statistical- Efficacy

There is no new efficacy information for this submission. The safety and efficacy of the FCDP product is supported in this application by Phase 3 trials that were submitted under the original canagliflozin NDA. In the canagliflozin program, six Phase 3 studies evaluated once-daily administration of canagliflozin 100 mg or 300 mg given once daily (QD) in subjects with T2DM on background metformin therapy (alone or in combination with other antidiabetic agents). These trials demonstrated that addition of canagliflozin to a stable maximally effective

dose of metformin improves glycemic control in subjects with type 2 diabetes. In addition, a factorial study used to support an indication for the combination of canagliflozin and metformin in drug naïve patients was submitted to the Invokamet NDA and approved (supplement 006).

Dr. Roberto Crackel provided a statistical review for the current submission. In his review he made reference to the statistical reviews for Invokana and Invokamet by Dr. Wei Liu (5 Sept 2013) and by himself (dated 7 Apr 2016). He states that the clinical trials section of the proposed product label for Invokamet XR tablets is identical to the clinical studies section of the approved product label for Invokamet tablets. The clinical data have been previously reviewed by the FDA, and therefore, there are no statistical issues. Details of the statistical reviews of the data supporting approval of this NDA can be found in the aforementioned reviews.

Please also see Dr. Kwon's primary clinical review for the current submission.

8. Safety

Safety data were reviewed in detail by Dr. Kwon for this NDA. The new safety information included data from:

- Safety data from cana/met XR-specific Phase 1 studies (DIA1041, DIA1062, DIA1063, DIA1044, DIA1042, and DIA1064);
- Safety data from extension phase of Phase 3 trials DIA3009 and DIA3010 (up to Week 104);
    - DIA3009 was a Phase 3, double-blind, randomized, active-controlled, 3-arm, parallel group, multicenter trial with a 104-week treatment period (52 week core period and additional 52-week extension period) to evaluate the efficacy, safety, and tolerability of canagliflozin compared to glimepiride in the treatment of subjects with T2DM with inadequate glycemic control on metformin monotherapy.
    - DIA3010 was a Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel group, multicenter trial with a 104-week treatment period (26-week core period followed by 78-week extension period) to evaluate the efficacy, safety, and tolerability of canagliflozin compared to glimepiride in the treatment of older subjects with T2DM with inadequate glycemic control on any glucose lowering therapy.
- Blinded subject listing including the number and proportion of randomized subjects who died, experienced a non-fatal serious adverse event, or who discontinued study drug due to an adverse event from January 1, 2013 through July 31, 2015 for five ongoing Phase 3/4 clinical trials (i.e., DNE 3001 [CREDENCE], DIA3008 [CANVAS], DIA4002, DIA4003 (CANVAS-R], and DIA4004), and for two Phase 2 trials (DIA2004 [Type 1 diabetes study] and OBE2002 [Obesity study in obese/overweight non-diabetic subjects]);
- Most recent Periodic Adverse Drug Experience Report (PADER) for canagliflozin and Cana/Met (reporting period June 29, 2015 to September 18, 2015) and Periodic Benefit

Risk Evaluation Report/Periodic Safety Update Report (PSUR) (reporting period November 16, 2014 to March 28, 2015);

- The most recent canagliflozin annual enhanced pharmacovigilance report (reporting period March 29, 2014 through March 28, 2015) supporting canagliflozin PMR 2027-3.
- 4MSU which included the following safety data with cutoff date of December 31, 2015:
  - Blinded subject listing for ongoing clinical studies through data cutoff of December 31, 2015 for the number of subjects randomized with treatment-emergent deaths, serious adverse events, and discontinuations due to adverse events including 2 Phase 1 studies (DIA1054 and DIA1055), 2 Phase 3 studies (DIA3008 [CANVAS] and DNE3001 [CREDENCE]) and 2 Phase 4 studies (DIA4003 [CANVAS-R] and DIA4004);
  - Summary of safety findings from recently completed clinical studies including a Phase 1 study (DIA1072), 2 Phase 2 studies (DIA2004 [in type 1 diabetes mellitus as add-on to insulin] and OBE2002 [in non-diabetic, obese subjects]), one Phase 4 study (DIA4002 [subjects with hypertension and T2DM]), and 2 Phase 1 BE studies (DIA1070 and DIA1071) that completed in March 2015;
  - Safety findings from the medical literature search from April 1, 2012 through December 31, 2015;
  - Summary of postmarketing experience with reference to the most recent Periodic Adverse Drug Experience Report (PADER) for canagliflozin and Cana/Met IR FDC (reporting period September 29, 2015 to December 28, 2015).

Based on review of these data, Dr. Kwon did not note any new or worsening safety issues. Please see her review for details.

Note that the 915 review (Postmarket Safety Summary) for Invokamet is ongoing, and any notable findings during this review would be applied to the current NDA if approved.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA.

10. Pediatrics

This NDA was discussed at the PeRC meeting on August 3, 2016. The PeRC agreed with the sponsor's plan for a partial waiver in patients 0 to less than 10 years of age because the studies are impossible and highly impractical and to a deferral in patients 10 years to 17 years of age. The PeRC agreed that the PMRs for canagliflozin already established can be used to fulfill PREA PMRs for this product.

11. Other Relevant Regulatory Issues

Dr. Kwon reviewed financial disclosure information and found no potential concerns. I agree with her assessment. One investigator reported a significant equity interest in (b) (6) in excess of $50,000. However, this investigator did not enroll any patients, and thus this potential financial interest would not affect the study results.

12. Labeling

A line-by-line labeling reviewed was conducted separately. Final agreed upon labeling was received by FDA on 20 Sep 2016. Specific labeling issues are listed below.

- For Invokamet XR, the same language will be used for the pregnancy and lactation subsections of the prescribing information (PI) as was used for Invokamet which previously underwent conversion to the Pregnancy and Lactation Labeling rule format during review and approval of an Efficacy Supplement (supplement 006 which provided for the initial therapy indication). Please see consult review from Dr. Mastroyannis for details which reviewed in tandem the proposed PLLR format labeling for Invokamet supplement 006 and the current NDA.

- The proprietary name Invokamet XR was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

- DMEPA provided an initial labeling review of the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors. DMEPA recommended that for the professional sample container labels, the size and prominence of the "sample-Not for Sale" statement be increased so that it is clear that these are drug samples, per 21CFR 203.38(c). The applicant submitted revised carton and container labeling which was found to be acceptable.

- The Office of Prescription Drug Promotion (OPDP) provided a written consult on the proposed draft labeling based on the version dated August 18, 2016; OPDP found the proposed PI acceptable.

- Comments on the Medication Guide (Med Guide) were provided in a collaborative review between DMPP (Patient Labeling) and OPDP. Review of the Invokamet XR Med Guide was based on the substantially complete PI version dated August 19, 2016. It was recommended to avoid using the term (b)(4) Otherwise, the Med Guide was found to be acceptable.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The applicant has demonstrated bioequivalence (BE) of canagliflozin/metformin extended release FDCP to co-administration of canagliflozin and metformin hydrochloride (HCl). Specifically, the pivotal BE studies (DIA1041, DIA1063, DIA1062, and DIA1044) demonstrated that the to-be-marketed cana/met XR tablet strengths of 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg, respectively were bioequivalent to the equal doses of the individual components. Efficacy of the proposed FCDP is supported by the previous approval of the NDAs for canagliflozin, canagliflozin/metformin, and metformin XR.

The safety review of these new Phase 1 BE studies, safety data from the extension period for DIA3009 and DIA3010, and updated postmarketing safety data including enhanced pharmacovigilance reporting and data from the 4-month safety update did not identify any new safety issues with use of the combination. There are no issues that change the overall risk/benefit assessment of the canagliflozin/metformin FDCP, and the cana/met XR formulation is acceptable for approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

See Pediatrics above

- Recommended Comments to Applicant

None

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/s/

LISA B YANOFF
09/20/2016

JEAN-MARC P GUETTIER
09/20/2016
I concur.