

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204353Orig1s000

CHEMISTRY REVIEW(S)

Final Addendum to Quality Reviews

To: NDA 204353 (canagliflozin/metformin hydrochloride)

Subject: Final ONDQA recommendation

The 10-FEB-2014 NDA Resubmission is in response to the 11-DEC-2013 CR letter. The CR letter did not include any pending issue or deficiency from the Quality reviews (CMC, Biopharmaceutics, and EES).

- The primary CMC reviewer (Sheldon Markofsky) confirmed that the resubmission contains no new CMC information and no CMC review of the resubmission is necessary (his previous CMC recommendation for this NDA was for approval). Labeling revisions were sent to the OND PM as part of the multi-disciplinary labeling review.
- The Biopharmaceutics review in DARRTS dated 10-MAR-2014 is for approval.
- The EES overall recommendation dated 25-APR-2014 for this NDA is ACCEPTABLE.

Conclusion:

Based on the CMC and Biopharmaceutics reviews and the Compliance overall findings, the ONDQA recommendation for this NDA is for APPROVAL.

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

/s/

SUONG T TRAN
05/12/2014

DANAE D CHRISTODOULOU
05/12/2014

NDA 204353

Invokamet
(Canagliflozin and metformin HCl) Tablets

Janssen Pharmaceuticals, Inc.

Sheldon Markofsky, Ph.D.

Division of Metabolism and Endocrine Products (HFD-510)

and

Office of New Drug Quality Assessment III Branch VII

File: 204353b

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	9
II. Summary of Chemistry Assessments	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used	11
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative	12
A. Reviewer's Signature	12
B. Endorsement Block	12
C. CC Block	12
Chemistry Assessment Starting on pp. 13	
I	
S DRUG SUBSTANCE	pp. 13
P DRUG PRODUCT	pp. 22
A APPENDICES (Attachments)	141
R REGIONAL INFORMATION	N/A
II. List Of Deficiencies To Be Communicated	none

Chemistry Review Data Sheet

1. NDA 204353
2. REVIEW #: 1
3. REVIEW DATE: 24-October-2013
4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	12-Dec-2012
Filing Review Document	08-Jan-2013
Amendment ^a	28-June-2013
Amendment ^b	13-Aug-2013
Amendment ^c	15-Aug-2013
IR Letter	06-June-2013
IR Letter	28-June-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	12-Dec-2012
Amendment ^a	28-June-2013
Amendment ^b	13-Aug-2013
Amendment ^c	15-Aug-2013

- a) The 6-28-13 amendment provides responses to our 6-6-13 Information Requests.
b) The 8-13-13 amendment provides responses to our 6-28-13 Information Requests.
c) The 8-15-13 amendment provides up-dated labeling information.

7. NAME & ADDRESS OF APPLICANT:

Name: Janssen Pharmaceuticals Inc. 1125
Address: 1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

Representative: Brandon D. Porter,
Global Regulatory Affairs
Telephone: (858) 784-3123

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Invokamet
- b) Non-Proprietary Name: Canagliflozin and metformin HCl Tablets
- c) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1 Type 1 NME and Type 4 New Combination
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

[The reference listed drug is Glucophage (metformin HCl tablets), NDA 20-357]

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY:

50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg and 50 mg/1000 mg
(canagliflozin/metformin hydrochloride)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

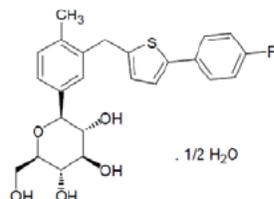
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Canagliflozin



Molecular formula: C₂₄H₂₅FO₅S•1/2 H₂O

Molecular weight: 453.53 [444.52 + (0.5 • 18.02)]

INN: Canagliflozin

USAN: Canagliflozin

Chemical names:

(Chemical Abstracts)

(1*S*)-1,5-anhydro-1-C-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol

(IUPAC)

(1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

CAS Registry Numbers: 928672-86-0 (hemihydrate)

842133-18-0 (anhydrous)

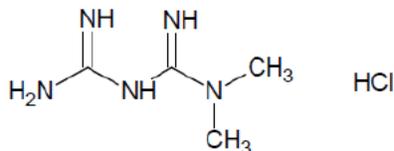
Company Code Numbers: R600348

JNJ-28431754-ZAE

TA-7284

In both the NDA and the Review, the terminology Canagliflozin and Canagliflozin hemihydrate is used interchangeably, unless otherwise noted.

Metformin HCl



Molecular formula: $C_4H_{11}N_5 \cdot HCl$

Molecular weight: 165.62

Chemical name(s):

1,1-Dimethylbiguanide hydrochloride

N,N-dimethylimidodicarbonimidic diamide hydrochloride

INN: Metformin Hydrochloride

(CAS) registry number: 1115-70-4

Company Code Numbers: JNJ-1158196-AAC

R024606

T002931

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	7	Adequate	1-15-13	Reviewed by Ryan Nguyen

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Comments:

An amendment to the DMF, received on 7-12-13, does not provide for any changes that would affect the quality of this drug substance.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	204042	Invokana (Canagliflozin Tablets)
IND	110545	Canagliflozin and Metformin HCl Tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATI ON	DATE	REVIEWER
EES	Acceptable	8-8-13	Office of Compliance
Pharm/Tox	Acceptable	8-21-13	Fred Alavi
Methods Validation	Acceptable	10-24-13	S. B. Markofsky
EA	Acceptable	10-13-13	James Laurenson
Microbiology	N/A		
ONDQA/Biopharm Review	Acceptable	7-26-13	Okpo Eradiri

19. ORDER OF REVIEW: N/A (OGD Only)

The Chemistry Review for NDA 204353

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) Drug Product

The drug product (Invokamet) consists of canagliflozin / metformin hydrochloride immediate-release (film-coated) tablets. The combination of canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, an antihyperglycemic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Canagliflozin and Metformin hydrochloride tablets are proposed to be marketed in 50 mg/500 mg, 50 mg/1000 mg, and 150 mg/500 mg and 150 mg/1000 mg strengths. Although the canagliflozin is a hemihydrate, the above noted tablet strengths are based on the anhydrous form of this drug substance. The metformin strength is based on its hydrochloride salt.

The 50 mg/500 mg tablets are:

Immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side

The 50 mg/1000 mg tablets are:

Immediate-release, capsule-shaped, beige film-coated tablets with “CM” on one side and “551” on the other side

The 150 mg/500 mg tablets are:

Immediate-release, capsule-shaped, yellow film-coated tablets with “CM” on one side and “215” on the other side

The 150 mg/1000 mg tablets are:

Immediate-release, capsule-shaped, purple film-coated tablets with “CM” on one side and “611” on the other side

All tablet strengths will be marketed in high density polyethylene bottles (HDPE) with desiccant.

Besides canagliflozin and metformin HCl, the drug product contains the following inactive ingredients in the core tablets: croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. In addition, the film coating contains the following excipients: Macrogol/PEG, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide yellow, (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red, (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000g tablets only), and iron oxide black, (150 mg/1,000 mg tablets only). All of the inactive ingredients are compendial.

2) Drug Substances

Canagliflozin

The drug substance, canagliflozin, is manufactured by Janssen Pharmaceutica NV in Belgium, and the relevant CMC issues related to the manufacture of this material are described in the Drug Substance section of the applicant’s approved and referenced NDA 204042 and in the Chemistry Reviews of NDA 204042.

Canagliflozin is

(b) (4)

The drug substance is soluble in many organic solvents but is insoluble in aqueous media (from pH 1.1 to 12.9). Janssen classifies this drug substance as a Class IV compound according to the Biopharmaceutical Classification System (BCS) because of its low solubility and low permeability. Satisfactory stability data was provided to support a retest date of (b) (4) months for the drug substance for storage at 25°C/60 % R.H. Accordingly, the drug substance is deemed adequate to support this NDA (204353).

Metformin Hydrochloride

Metformin hydrochloride is manufactured by (b) (4). Janssen referenced DMF (b) (4) for the manufacturing details and other CMC information related to the metformin HCl drug substance, and based on the latest up-dates and chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (204-353). The specification and testing procedures for this drug substance also comply with

the USP monograph for metformin HCl.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose is 50 mg canagliflozin with 500 mg metformin (or the patient's current dose of metformin) twice daily with foods. A starting dose can be increased to 150 mg canagliflozin; and the current dose of metformin twice daily should be considered in patients tolerating Invokamet with 50 mg canagliflozin and the current dose of metformin twice daily with foods. The stability studies support an expiration-dating period of 24 months for all strengths of Invokamet when stored at controlled room temperature [25°C (77°F)], with excursions permitted between 15°C and 30°C (59-86° F) packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.

C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved on the following basis:

- Adequate information was provided in the NDA for the synthesis, (b) (4) and controls of the drug substance
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product
- An acceptable Establishment Report for the relevant manufacturing and testing facilities.
- An acceptable Environmental Assessment

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

III. Administrative

A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

131 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHELDON B MARKOFSKY
10/28/2013

DANAE D CHRISTODOULOU
10/28/2013

I agree with the reviewer's conclusion and recommendations

CMC Filing

NDA 204353
Applicant: Janssen Pharmaceuticals Inc.
Stamp Date: 12-DEC-2012
PDUFA Date: 12-DEC-2013
Established Name: Canagliflozin and metformin hydrochloride
Proposed Proprietary Name: [none indicated]
Dosage form and strength: Tablet, 50/500, 150/500, 50/1000, 150/1000
(canagliflozin anhydrous/metformin HCl)
Route of Administration: Oral
Indications: Treatment of type 2 diabetes

CMC Lead: Su (Suong) Tran

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Recommended Consults

EES	EER to be submitted to OMPQ by ONDQA PM.
Pharm/Tox	Same review of genotoxic impurities as for referenced NDA 204042.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
EA	<i>The categorical exclusion claim will be assessed by Primary Reviewer.</i>

4 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
1.	Is the CMC section organized adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

CMC Filing

9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
18.	Has stability data and analysis been provided for the drug substance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
28.	Have any biowaiver been requested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

CMC Filing

G. METHODS VALIDATION (MV)					
	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
H. MICROBIOLOGY					
	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
I. LABELING					
	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

This document will be signed in DARRTS by the following:

CMC Lead
Branch Chief

{See appended electronic signature page}

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

/s/

SUONG T TRAN
01/08/2013

ALI H AL HAKIM
01/08/2013