

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210874Orig1s000

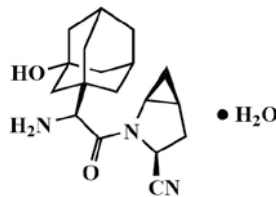
PRODUCT QUALITY REVIEW(S)



Labeling Addendum to NDA 210874

The API saxagliptin (b) (4) the revised language pertaining to saxagliptin is in Section 11 'DESCRIPTION' of the label has been revised as follows:

Saxagliptin is an active inhibitor of the dipeptidyl-peptidase-4 (DPP-4) enzyme. It is isolated in the monohydrate form chemically known as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is C₁₈H₂₅N₃O₂•H₂O and the molecular weight is 333.43. The structural formula is:



Furthermore, as the above structural formula clearly indicates that the API (b) (4) Therefore, the description of the 4 individual strengths of the drug product now contain a revised statement for saxagliptin: “exists in the form of HCl salt” (b) (4). The description of the four strengths of the drug product is now as follows:

- QTERNMET XR is available as film-coated tablets of four strengths:
- 2.5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 2.5 mg dapagliflozin (equivalent to 3.08 mg dapagliflozin propanediol), 2.5 mg saxagliptin (exists in the form of HCl salt), and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).
 - 5 mg dapagliflozin/2.5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 5 mg dapagliflozin (equivalent to 6.15 mg dapagliflozin propanediol), 2.5 mg saxagliptin (exists in the form of HCl salt) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).
 - 5 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 5 mg dapagliflozin (equivalent to 6.15 mg dapagliflozin propanediol), 5 mg saxagliptin (exists in the form of HCl salt)) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).
 - 10 mg dapagliflozin/5 mg saxagliptin/1000 mg metformin HCl: Each tablet contains 10 mg dapagliflozin (equivalent to 12.3 mg dapagliflozin propanediol), 5 mg saxagliptin (exists in the form of HCl salt)) and 1000 mg metformin HCl (equivalent to 779.86 mg metformin).

**Christopher
Galliford -S**

Digitally signed by Christopher Galliford -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001708703,
cn=Christopher Galliford -S
Date: 2019.04.24 12:09:42 -04'00'

Christopher Galliford ATL

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/

CHRISTOPHER GALLIFORD
04/30/2019 03:04:58 PM

Recommendation:
NDA: Approval

NDA 210874 Review 1

Drug Name/Dosage Form	Qtemmet, Dapagliflozin, saxagliptin and metformin hydrochloride extended release tablets (Dapa/Saxa/Met XR)
Strength	Dapa/Saxa/Met XR 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ASTRAZENECA AB

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	07/02/2018
0002	07/26/2018
0013	12/28/2018
0015	01/11/2019
0016	01/22/2019
0017	02/14/2019

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal	OPQ/ONDP/DNDAPI/NDBI
Drug Product	Christopher Galliford	OPQ/ONDP/DNDPII/NDPBVI
Process	Ted Chang	OPQ/OPF/DPAII/PABIV
Facility	Ted Chang	OPQ/OPF/DPAII/PABIV
Biopharmaceutics	Sarah Ibrahim	OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Anika Lalmansingh	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Christopher Galliford	OPQ/ONDP/DNDPII/NDPBVI
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA

¹Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	202293	Dapagliflozin (Farxiga® Tablets)
NDA	205649	Dapagliflozin/ Metformin hydrochloride (Xigduo™ XR Tablets)
NDA	22350	Saxagliptin (Onglyza® Tablets)
NDA	200678	Saxagliptin/Metformin hydrochloride (Kombiglyze® XR Tablets)
NDA	209091	Dapagliflozin/Saxagliptin (Qtem® Tablets)

2. CONSULTS:

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 210874 is recommended for approval from a CMC perspective. There are no outstanding deficiencies and the manufacturing facilities have an approval recommendation. Labeling comments will be negotiated through the clinical project manager. A 24-month shelf-life will be granted through the approval letter based on stability data at intermediate storage conditions. The product should be stored below 30 °C (86 °F).

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

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The Qternmet XR tablets are fixed combination drug product (FCDP) XR extended release tablets that contain three drug substances dapagliflozin, saxagliptin and metformin hydrochloride (Dapa/Saxa/Met). The three drug substances are described below:

Dapagliflozin propanediol monohydrate, 2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-Chloro-3-(4-ethoxybenzyl) phenyl]-6-(hydroxymethyl) tetrahydro-2*H*pyran-3,4,5-triol, (2*S*)-propane-1,2-diol (1:1) monohydrate is a non-hygroscopic, white to off-white crystalline powder which exhibits no polymorphism. Dapagliflozin has a solubility of 1.6 mg/mL. Manufacturing, packaging, quality control testing and release of dapagliflozin drug substance are performed a (b) (4)

(b) (4)The dapagliflozin drug substance is considered satisfactory based on the approved status of NDA 202293.

Saxagliptin, (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.1^{3,7}] dec-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile monohydrate, is a white to light yellow or light brown powder. Saxagliptin dehydrates before melting and its aqueous solubility at 24°C ± 3°C is 17.6 mg/mL. Manufacturing, packaging, quality control testing and release of saxagliptin drug substance are performed at:

(b) (4)
The saxagliptin drug substance is considered satisfactory based on the approved status of NDA 22350.

Metformin hydrochloride, 1,1-Dimethylbiguanide hydrochloride, is a white crystalline solid with an absence of polymorphism that is freely soluble in water and slightly soluble in alcohol. Manufacturing, packaging, quality control testing

and release of saxagliptin drug substance are performed a (b) (4)
 (b) (4)
 (b) (4). The metformin hydrochloride drug substance is considered satisfactory based on the approved status of NDA 202293.

B. Drug Product [QTERNMET™] Quality Summary

Dapagliflozin, saxagliptin and metformin hydrochloride extended release tablets (Dapa/Saxa/Met XR) are manufactured in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg. Descriptions of the various tablet strengths are reproduced below:

Tablet strength	Description
2.5/2.5/1000 mg	A light brown to brown biconvex, oval, film coated tablet, with "3001" debossed on one side.
5/2.5/1000 mg	A green biconvex, oval, film coated tablet, with "3002" debossed on one side.
5/5/1000 mg	A pink biconvex, oval, film coated tablet, with "3003" debossed on one side.
10/5/1000 mg	A grey biconvex, oval, film coated tablet, with "3004" debossed on one side.

The applicant has drawn from their considerable experience in the manufacture of approved combinations of these drug substances (b) (4)
 (b) (4)
 (b) (4)
 (b) (4)

Figure 2 Schematic illustration^a of the formulation design principle of the Dapa/Saxa/Met XR tablet.



^a Schematic illustration, not according to scale

The drug substances are the same dose and form as those found in currently approved drugs from the same applicant. This includes combination tablets of two of the three APIs used in this application. These combinations are QTERN® (dapagliflozin/saxagliptin) KOMBIGLYZE® XR (saxagliptin/metformin HCl XR),

and XIGDUO XR® (dapagliflozin and metformin hydrochloride XR). The drug product is a tablet dosage form for oral administration that combines Dapa/Saxa/Met XR. Long-term stability has been demonstrated when the product is packaged in high-density polyethylene (HDPE) bottles for commercial distribution.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Qternmet™
Non Proprietary Name of the Drug Product	Dapagliflozin, saxagliptin and metformin hydrochloride (Dapa/Saxa/Met)
Non Proprietary Name of the Drug Substance	Dapagliflozin, saxagliptin and metformin hydrochloride (Dapa/Saxa/Met)
Proposed Indication(s) including Intended Patient Population	Indicated for use in the treatment of patients with type 2 diabetes mellitus (T2DM)
Duration of Treatment	As directed by physician
Maximum Daily Dose	Dapa/Saxa/Met XR 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg
Alternative Methods of Administration	None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Christopher Galliford -S

Digitally signed by Christopher Galliford -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
 0.9.23.42.19200300.100.1.1=2001708703, cn=Christopher Galliford -S
 Date: 2019.03.26 14:50:29 -04'00'

Table of Contents

Chapter I: Drug Substance
Chapter II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics

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

R.2 Comparability Protocols

No comparability protocols are proposed in this application.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT**Reviewer's Assessment and Signature:**

ADEQUATE

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant states that this submission qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) and 25.15. To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

Reviewer's Assessment:

For two of the ingredients, dapagliflozin and saxagliptin, the applicant submitted claims for categorical exclusions from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included use amounts that were consistent with the claim and included the required statement of no extraordinary circumstances in accordance with 21 CFR 25.15. The CDER EA Team reviewed the claims and agreed that there are no extraordinary circumstances. Therefore, the claims for an exclusion from an EA for these substances are acceptable.

For metformin, the applicant provided an EA rather than a claim for an exclusion from an EA because, they stated, use is predicted to result in an EIC > 1 ppb. The EA Team, however, has determined that this substance already is > 1 ppb, and that

approval would not result in an increased use because the indication for this NDA is for treating patients who are inadequately controlled on metformin using identical doses of this substance (CTD section 2.2, Introduction). Thus, this substance is subject to a categorical exclusion from an EA in accordance with 21 CFR 25.31(a), which is for actions that do not increase the use of the active moiety. FDA also notes that while approval would not result in extraordinary circumstances, the data submitted by the applicant and in the open literature indicate that cumulative effects from all uses of metformin indicate the need for additional monitoring by FDA of these risks outside of the subject action, such as through future information collections and environmental assessments.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

ADEQUATE

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

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

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	QTERNMET XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended release tablets for oral use.	Adequate accepted by DMEPA
Dosage form, route of administration	tablets for oral use	Adequate
Controlled drug substance symbol (if applicable)	Not required	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(Dapa/Saxa/Met XR) in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg	Adequate

Conclusion: Adequate

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(Dapa/Saxa/Met XR) in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	tablets	Adequate
Strengths: in metric system	(Dapa/Saxa/Met XR) manufactured in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Dapagliflozin, saxagliptin and metformin hydrochloride extended release tablets (Dapa/Saxa/Met XR) for oral administration in the strengths of: 2.5/2.5/1000 mg as a light brown to brown biconvex, oval, film coated tablet, with “3001” debossed on one side. 5/2.5/1000 mg A green biconvex, oval, film coated tablet, with “3002” debossed on one side. 5/5/1000 mg as a pink biconvex, oval, film coated tablet, with “3003” debossed on one side. 10/5/1000 mg A grey biconvex, oval, film coated tablet, with “3004” debossed on one side.	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

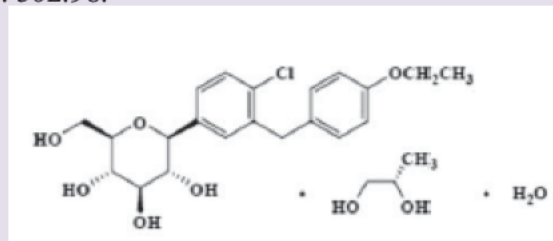
QTERNMET XR tablets for oral use is an extended-release formulation and contains dapagliflozin, saxagliptin, and metformin hydrochloride. There are four strengths:

- Each film-coated tablet contains dapagliflozin 10 mg (equivalent to 12.3 mg dapagliflozin propanedio (b)(4)), saxagliptin 5 m (b)(4), and metformin hydrochloride 1000 mg.
- Each film-coated tablet contains dapagliflozin 5 mg (equivalent to 6.15 mg dapagliflozin propanedio (b)(4)), saxagliptin 5 mg (b)(4), and metformin hydrochloride 1000 mg.
- Each film-coated tablet contains dapagliflozin 2.5 mg (equivalent to 3.08 mg dapagliflozin propanedio (b)(4)), saxagliptin 2.5 mg (b)(4), and metformin hydrochloride 1000 mg.
- Each (b)(4) tablet contains dapagliflozin 5 mg (equivalent to 6.15 mg dapagliflozin propanedio (b)(4)), saxagliptin 2.5 mg (b)(4), and metformin hydrochloride 1000 mg.

Inactive ingredients: The product contains carboxymethyl cellulose sodium, crospovidone, hypromellose 2208, iron oxides, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, macrogol/polyethylene glycol, silicon dioxide, talc, and titanium dioxide.

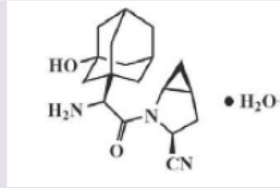
Dapagliflozin

Dapagliflozin is an active inhibitor of sodium-glucose cotransporter 2 (SGLT-2). Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). Empirical formula: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$. Molecular weight: 502.98.

**Saxagliptin**

Saxagliptin is an active inhibitor of the dipeptidyl-peptidase-4 (DPP-4) enzyme. Saxagliptin is described chemically as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. Empirical formula: $C_{18}H_{25}N_3O_2 \cdot H_2O$. Molecular weight: 333.43.

(b) (4)



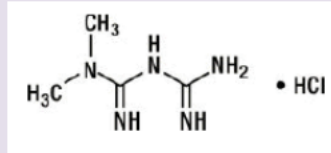
Metformin hydrochloride

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) (b) (4) molecular formula of C₄H₁₁N₅•HCl and a molecular weight of 165.63 (b) (4)

(b) (4)

(b) (4) The

structural formula is:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	Not required	Adequate
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	Not required	Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(Dapa/Saxa/Met XR) in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 5, 10, 30 or 60 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided	Adequate
Storage conditions	Provided	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	AstraZeneca Pharmaceuticals LP Wilmington, DE 19850	Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

Container labels are reproduced from the application below:

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence) (21 CFR 201.10(g)(2))	QTERNMET XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended release tablets for oral use.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(Dapa/Saxa/Met XR) manufactured in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg	Adequate
Route of administration (21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	30 or 60 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) (21CFR 201.100(b)(5)**)	Not required for an oral dosage form	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Warnings	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Carton Labeling

The drug product is supplied only in bottles, there is no secondary packaging.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	QTERNMET XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended release tablets for oral use.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	(Dapa/Saxa/Met XR) manufactured in strengths of 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg	Adequate
Net contents (21 CFR 201.51(a))	5, 10,30 or 60 tablets	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not required for an oral dosage form	Adequate
Sterility Information (if applicable)	Space is provided	Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
“See package insert for dosage information” (21 CFR 201.55)	Provided	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	Not included	Adequate

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	Adequate

Conclusion: There is no carton for the drug product, it is provided only in the bottles described above. As there is no need for secondary packaging, this is adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

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

BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of QTERNMET XR dapagliflozin/saxagliptin/metformin hydrochloride extended-release fixed combination drug product indicated for Type 2 Diabetes Mellitus. QTERNMET XR (dapagliflozin, saxagliptin and metformin hydrochloride) extended release tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4)

**Planned Tablet Strengths, Dosage and Daily Dose of Dapa/Saxa/Met XR
(dapagliflozin/saxagliptin/metformin^a XR)****Planned Tablet Strengths - dapagliflozin/saxagliptin
/metformin XR (mg)**

	Dosage	Daily Dose dapagliflozin/saxagliptin /metformin XR (mg)
5/5/1000	1 tablet once a day	5/5/1000
10/5/1000	1 tablet once a day	10/5/1000
2.5/2.5/1000	2 tablets once a day	5/5/2000
5/2.5/1000	2 tablets once a day	10/5/2000

^a Strengths and doses of metformin are given as amount of metformin hydrochloride. XR Extended Release

NDA: 210874

Drug Product Name / Strength: QTERNMET XR dapagliflozin/saxagliptin/metformin hydrochloride extended-release fixed combination drug product, 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg.

Route of Administration: Oral

Applicant Name: AstraZeneca Pharmaceuticals LP

Review Summary:

AstraZeneca (Sponsor) has developed a triple fixed combination drug product (FCDP) containing dapagliflozin, saxagliptin and metformin hydrochloride extended release (XR) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4)

(b) (4)

The formulation design principl

(b) (4)

(b) (4)

(b) (4)

Dapagliflozin, saxagliptin and metformin hydrochloride extended release tablets (Dapa/Saxa/Met XR) were developed based on the commercial products XIGDUO XR (dapagliflozin and metformin HCl XR, approved in the US 2014) and ONGLYZA (saxagliptin, approved in the US 2009). Knowledge from the development of the commercial combination products, QTERN (dapagliflozin and saxagliptin, approved in the US 2017) and KOMBIGLYZE XR (saxagliptin and metformin HCl XR, approved in the US 2010), was also considered since they build on the same drug substances and formulation design principles.

The drug release profile expecte

(b) (4)

(b) (4)

The Applicant proposes to use the same dissolution method that was previously approved for the ONGLYZA and XIGDUO XR. The Applicant adequately justified the dissolution method parameters for the proposed extended-release tablet product. The acceptance criteria for dissolution of dapagliflozin and metformin HCl in Dapa/Saxa/Met XR is consistent with the requirements for dissolution of dapagliflozin and metformin HCl in XIGDUO XR. The Dapa/Met XR core used for manufacture of Dapa/Saxa/Met XR is the same as used in XIGDUO XR (strengths of 2.5/1000 mg, 5/1000 mg and 10/1000 mg) and the dissolution method used for Dapa/Saxa/Met XR is identical to the method used for XIGDUO XR (USP Apparatus 1 (b) (4) baskets) at 100 rpm in 1000 mL of pH 6.8 potassium phosphate buffer (50 mM)), refer to NDA 205,649 for XIGDUO XR. The acceptance criterion for dissolution of saxagliptin in

Dapa/Saxa/MetXR is consistent with the requirements for dissolution of saxagliptin in ONGLYZA®, refer to NDA 22350 for ONGLYZA. The dissolution methods used for the two products are different, USP Apparatus 1 (baskets) is used for Dapa/Saxa/Met XR and USP Apparatus 2 (paddles) is used for ONGLYZA. In vitro dissolution for saxagliptin and dapagliflozin from Dapa/Saxa/Met XR 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg tablets was rapid in all test dissolution media, with ^(b)₍₄₎% dissolved in 30 minutes.

Dissolution data submitted support the proposed dissolution acceptance criteria. The Applicant’s proposed dissolution acceptance criteria are acceptable.

In vitro alcohol interaction studies was conducted for this particular finished drug product as per agency’s request, and the data indicate a decrease in metformin release with increase in alcohol concentration particularly above 40% ethanol.

Requests for biowaivers for the remaining two Dapa/Saxa/Met XR tablet strengths, 2.5/2.5/1000 mg and 5/5/1000 mg are **adequate pending** acceptable outcome of BE studies and dose proportionality with therapeutic dose range per clinical pharmacology review (please refer to clinical pharmacology review for additional details).

From the Biopharmaceutics perspective, NDA 210874 for QTERNMET XR Dapagliflozin/saxagliptin/metformin hydrochloride extended-release fixed combination drug product, 2.5/2.5/1000 mg, 5/2.5/1000 mg, 5/5/1000 mg and 10/5/1000 mg is recommended for **approval pending** acceptable outcome of BE studies and dose proportionality with therapeutic dose range per clinical pharmacology review (please refer to clinical pharmacology review for additional details).

List Submissions being reviewed (table):

Date of Submission	Purpose of Submission
July 2, 2018	Original
January 11, 2019	S0015
February 11, 2019	S0017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer’s Assessment: N/A for modified release products

Dapagliflozin and Saxagliptin components are immediate release in the proposed finished drug product. Dapagliflozin is a non-ionizable compound; thus, its aqueous solubility and partition coefficient are not affected by changes in pH. The aqueous solubility of dapagliflozin is 2.1 mg/mL across the pH range of 1.2 to 6.8 at 37°C. Dapagliflozin is highly permeable in in vitro intestinal permeability models. The absolute oral bioavailability of dapagliflozin is high (78%) and it has dose proportional pharmacokinetics (PK) ranging from 0.1 mg to 500 mg following

oral administration. Based on these data, dapagliflozin is a BCS Class 3 compound (with high solubility/<90% absolute oral bioavailability as per the BCS).

The aqueous solubility of saxagliptin is variable with pH, ranging between 17.6 mg/mL and 149 mg/mL in the physiological pH interval. At the highest dose strength of 5 mg, the dose/solubility is less than 1 mL, making saxagliptin a high solubility compound (as per the BCS). As a result, absorption of saxagliptin is not expected to be limited by its aqueous solubility or dissolution at physiological pH values. Based upon its aqueous solubility and its permeability in the Caco-2 system, saxagliptin would be designated a BCS Class 3 compound.

The firm provided their rationale for Dapagliflozin having characteristics as high solubility/high in vitro permeability and at least 78% absorbed from the gastrointestinal tract with linear pharmacokinetics, which makes it BCS Class 1-like rather than BCS Class 3.

Dissolution Method and Acceptance Criteria

Reviewer’s Assessment: ADEQUATE

Dissolution Method:

The proposed dissolution method is described in the following table:

Dissolution parameters

Parameter	Setting
Dissolution Apparatus	USP Apparatus 1 (baskets, 20-Mesh)
Dissolution Medium	50 mM potassium phosphate buffer, pH 6.8
Dissolution Medium Volume	1000 mL
Temperature in Vessel	37°C
Rotation Speed	100 rpm
Sampling Time for dapagliflozin	30 minutes
Sampling Time for saxagliptin	30 minutes
Sampling Time for metformin hydrochloride	60, 180 and 600 minutes

(b) (4)

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

- The dissolution method is adequate.
- Dissolution profiles for all commercial tablet strengths using the final dissolution method are shown below. These tablet lots were used in the registration stability study.

Batch results for Dapa/Saxa/Met XR film coated tablets 2.5/2.5/1000 mg

Batch number		HK0155	HK0156	HN0158
Test	Acceptance criteria	Results	Results	Results
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	97 (95-100)	99 (97-100)	94 (93-96)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	101 (97-103)	101 (95-106)	101 (95-106)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4) of label claim after 1 h	27 (26-28)	26 (26-27)	26 (26-27)
		55 (55-56)	54 (53-56)	54 (54-55)
		93 (92-94)	93 (91-94)	94 (92-95)

Batch number		JF0259	JF0260	JF0261
Test	Acceptance criteria	Results	Results	Results
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	95 (93-97)	99 (96-100)	98 (95-100)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	100 (96-102)	97 (94-98)	100 (95-105)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4) of label claim after 1 h	26 (26-27)	27 (26-27)	26 (26-27)
		55 (54-56)	55 (55-55)	55 (55-56)
		91 (90-92)	91 (90-91)	92 (92-93)

Batch results for Dapa/Saxa/Met XR film coated tablets 5/2.5/1000 mg

Batch number		HK0157	HK0158	HK0159
Test	Acceptance criteria	Results	Results	Results
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	95 (92-98)	94 (90-96)	96 (93-98)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	101 (97-106)	102 (98-108)	101 (96-106)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4) of label claim after 1 h	27 (27-28)	27 (26-28)	27 (27-28)
		56 (55-57)	56 (55-56)	56 (55-57)
		94 (93-95)	94 (92-95)	94 (93-95)

Batch number		JN0143	JN0145
Test	Acceptance criteria	Results	Results

Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	95 (93-97)	95 (91-101)	
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	101 (98-109)	103 (99-113)	
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4)			
	of label claim after 1 h	26 (25-27)	27 (27-28)	
	of label claim after 3 h	54 (54-55)	56 (55-56)	
	of label claim after 10 h	92 (91-93)	94 (93-95)	

Batch results for Dapa/Saxa/Met XR film coated tablets 5/5/1000 mg

Batch number		HK0163	HN0159	HN0488
Test	Acceptance criteria	Results	Results	Results
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	96 (93-98)	95 (89-98)	93 (86-98)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	99 (97-101)	100 (98-104)	102 (98-104)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4)			
	of label claim after 1 h	27 (27-27)	26 (26-27)	27 (26-27)
	of label claim after 3 h	56 (55-56)	54 (54-55)	56 (55-57)
	of label claim after 10 h	94 (93-94)	93 (92-94)	95 (94-96)

Batch results for Dapa/Saxa/Met XR film coated tablets 10/5/1000 mg

Batch number		HK0164	HK0165	HK0166
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	92 (89-95)	93 (90-97)	95 (91-100)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	102 (99-105)	103 (101-107)	102 (97-105)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4)			
	of label claim after 1 h	27 (27-28)	27 (27-27)	27 (27-28)
	of label claim after 3 h	56 (55-56)	56 (55-56)	56 (55-56)
	of label claim after 10 h	93 (92-94)	94 (93-94)	94 (93-95)

Batch number		JF0262	JF0263	JF0264
Test	Acceptance criteria	Results	Results	Results
Dissolution				
Dapagliflozin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	98 (94-100)	96 (93-98)	94 (90-101)
Saxagliptin, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes	97 (95-99)	96 (91-101)	98 (94-99)
Metformin hydrochloride, Mean (Min-Max)	Shall comply with the requirements in USP/Ph Eur, (b)(4)			
	of label claim after 1 h	27 (26-27)	27 (26-27)	26 (26-27)
	of label claim after 3 h	55 (54-56)	55 (54-56)	55 (54-55)
	of label claim after 10 h	92 (91-92)	91 (91-92)	91 (91-92)
Uniformity of dosage units				

Acceptance Criteria:

- The Applicant proposed the following dissolution acceptance criteria:
 - Dapagliflozin: Shall comply with the requirements in USP/Ph Eur, Q=(b)(4)% at 30 minutes
 - Saxagliptin: Shall comply with the requirements in USP/Ph Eur, Q=(b)(4) at 30 minutes
 - Metformin hydrochloride: Shall comply with the requirements in USP/Ph Eur,

(b) (4)
of label claim after 1 h
of label claim after 3 h
of label claim after 10 h

- The dissolution method used at the time of release testing for the primary stability batches used sinkers and this data is provided in Section 3.2.P.5.4 Batch Analysis. The data provided supports the proposed dissolution acceptance criteria.
- **The dissolution acceptance criteria are acceptable.**

Clinical relevance of dissolution method & acceptance criteria (IVIVC)**Reviewer's Assessment: NA**

- The Applicant did not attempt to develop and validate the IVIVC model.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping**Reviewer's Assessment: INADEQUATE**

- No studies were conducted to evaluate the effect of alcohol on in vitro dissolution of metformin hydrochloride (HCl) XR in the original submission.
- Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency requested in an information request dated December 11, 2018 that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:
 - Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 1 (Basket) @100 rpm, with or without alcohol;
 - Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours
 - Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
 - Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
 - Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
- The firm responded by submitting In vitro alcohol interaction studies performed on Xigduo® XR and approved by US FDA in 29 October 2014 and included (b) (4) (b) (4) The included in vitro dissolution data on Xigduo® XR 10/1000 mg was obtained at pH 6.8 with 0, 5, 10, or 25% ethanol (v/v) in the dissolution medium. The firm thereafter, submitted In vitro dissolution data were generated on the highest Dapa/Saxa/Met XR FCDP tablet strength (10/5/1000 mg, batch HK0164) in the current NDA, using the QC dissolution method at pH 6.8, with 25% or without ethanol in the media.
- A follow up information request was sent to the firm explaining that the current practice is to conduct alcohol dose dumping as described under the information request dated December 11, 2018. The following information request was conveyed to the firm January 18, 2019:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 1 (Basket) @100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

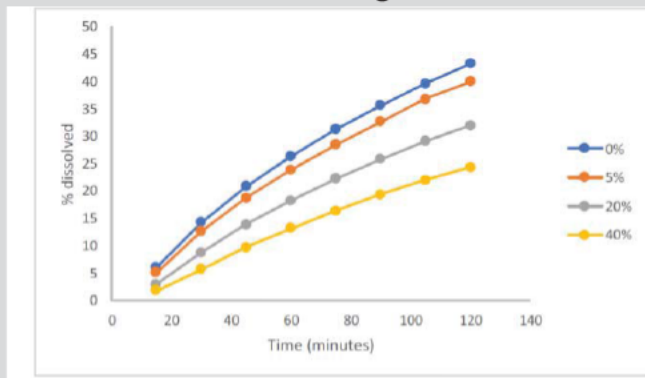
Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

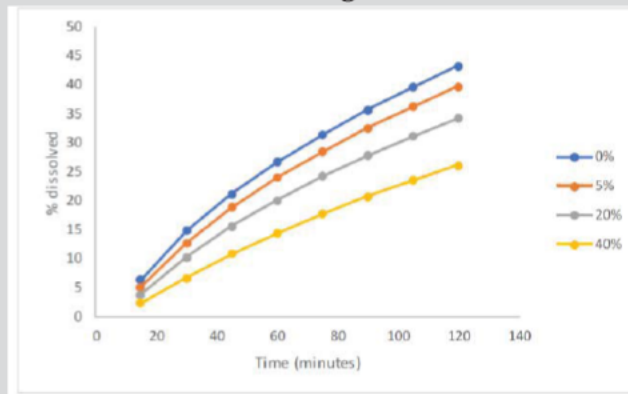
Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

- The information submitted on February 11, 2019 under S0017 included the required data and summarized in the figure below:

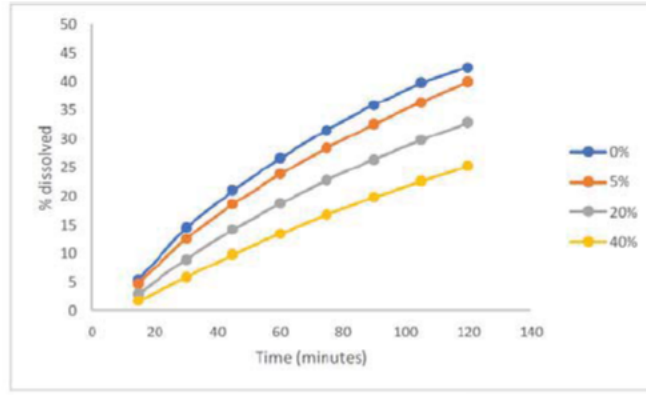
- Metformin average percent dissolved versus time in 0.1 N HCl with 0, 5, 20 and 40 % ethanol (v/v) from Dapa/Saxa/Met XR 10/5/1000 mg.



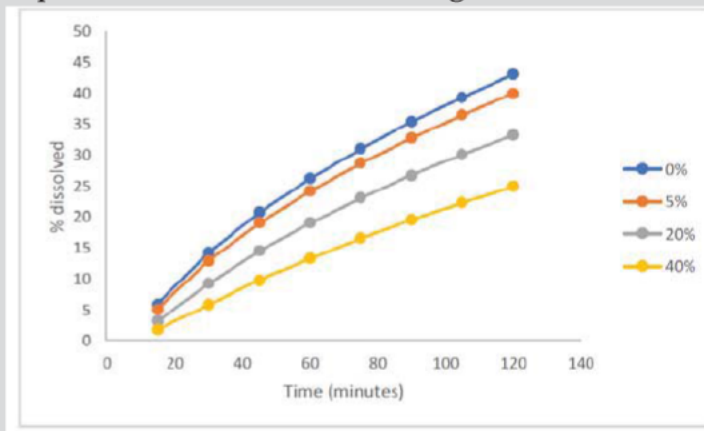
- Metformin average percent dissolved versus time in 0.1 N HCl with 0, 5, 20 and 40 % ethanol (v/v) from Dapa/Saxa/Met XR 5/5/1000 mg.



- Metformin average percent dissolved versus time in 0.1 N HCl with 0, 5, 20 and 40 % ethanol (v/v) from Dapa/Saxa/Met XR 5/2.5/1000 mg.



- Metformin average percent dissolved versus time in 0.1 N HCl with 0, 5, 20 and 40 % ethanol (v/v) from Dapa/Saxa/Met XR 2.5/2.5/1000 mg.



- This Reviewer calculated the following f2 calculations per the in vitro alcohol interaction data:

Strength	% EtOH (v/v)	F2
10/5/1000 mg	0% vs. 5%	80
	0% vs. 20%	54
	0% vs. 40%	42
5/5/1000 mg	0% vs. 5%	76
	0% vs. 20%	58
	0% vs. 40%	44
5/2.5/1000 mg	0% vs. 5%	78
	0% vs. 20%	55
	0% vs. 40%	43
2.5/2.5/1000 mg	0% vs. 5%	81
	0% vs. 20%	56
	0% vs. 40%	44

- The f2 values greater than 50 indicate the dissolution profiles with 0% Ethanol are similar to profiles with 5 and 20% Ethanol, however, f2 values for 40% Ethanol indicates that the

dissolution profiles with are not similar and the dissolution rate decreases with increase in alcohol concentration.

- Therefore, the in vitro alcohol interaction studies suggest that there is evidence of alcohol dose effect on release.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer’s Assessment: ADEQUATE

The Applicant submitted the following to support the extended release designation claim per 21 CFR 320.25(f):

1. The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

- Dissolution testing of the drug product using the proposed dissolution method (b) (4) pH 6.8 phosphate buffer, did not show any evidence of in vitro dose dumping.
- Following the administration of 5/2.5/1000 mg Dapa/Saxa/Met XR, median tmax value for metformin was slightly delayed under fed (5.98 hours) versus fasted (4.00 hours) state:

Parameter (Unit)		Treatment A (n = 41)	Treatment B (n = 41)	Treatment C (n = 41)
AUC (h*ng/mL)	Geometric Mean	10980 ^a	10930 ^b	9511 ^c
	(CV%)	(32.82)	(34.44)	(26.11)
AUC _(0-t) (h*ng/mL)	Geometric Mean	10910	10780	9265
	(CV%)	(31.03)	(34.20)	(26.62)
C _{max} (ng/mL)	Geometric Mean	1041	1098	1195
	(CV%)	(29.47)	(26.97)	(28.04)
t _{max} (h)	Median	5.98	5.98	4.00
	(Min, Max)	(3.98, 8.02)	(3.98, 8.05)	(1.52, 6.00)
t _{1/2z} (h)	Arithmetic Mean	15.37 ^a	17.00 ^b	16.72 ^c
	(SD)	(10.10)	(13.39)	(11.53)

CV% = coefficient of variation (percentage); FCDP = fixed-combination drug product; n = number of subjects in the given category; SD = standard deviation; XR = extended-release

A = Single dose of 2.5 mg saxagliptin (ONGLYZA) and 5 mg dapagliflozin/1000 mg metformin XR (XIGDUO XR) tablets co-administered orally under fed condition;

B = Single dose of triple FCDP consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fed condition;

C = Single dose of triple FCDP tablet consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fasted condition.

^a n=35. ^b

n=37. ^c

n=39.

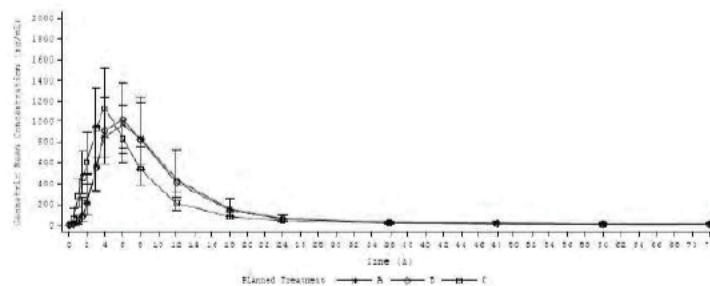
Data Source: Table 14.2.2.1

2. The drug product’s steady-state performance is equivalent to a currently marketed extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.

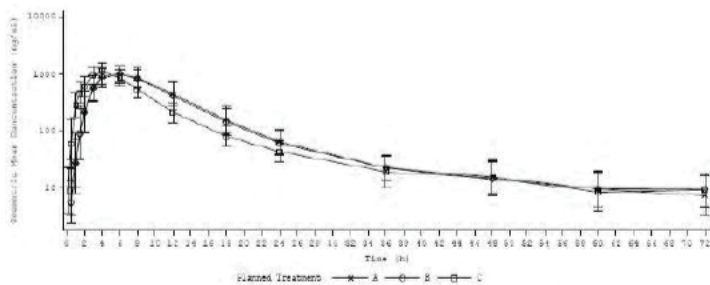
Parameter (unit)	Treatment	n	Geometric LS Mean	Geometric Mean Ratio (%) ^a	90% CI ^a
Bioequivalence Assessment (B/A)					
AUC (h ⁺ ng/mL)	B	37	10930	99.48	(88.21, 112.19)
	A	35	10990		
AUC _(0-∞) (h ⁺ ng/mL)	B	41	10790	98.89	(88.51, 110.49)
	A	41	10910		
C _{max} (ng/mL)	B	41	1098	105.45	(95.24, 116.76)
	A	41	1041		
Food Effect Assessment (B/C)					
AUC (h ⁺ ng/mL)	B	37	10930	114.96	(102.26, 129.24)
	C	39	9506		
AUC _(0-∞) (h ⁺ ng/mL)	B	41	10790	116.40	(104.18, 130.06)
	C	41	9266		
C _{max} (ng/mL)	B	41	1098	91.79	(82.90, 101.63)
	C	41	1196		

A single-dose administration of saxagliptin/dapagliflozin/metformin 2.5/5/1000 mg XR FCDP under fed state, mean plasma concentration-time profile for metformin was almost superimposable to that following co-administration of the individual components (ONGLYZA® and XIGDUO® XR) under fed-state.

Linear scale



Semi-logarithmic scale



FCDP = fixed-combination drug product; GSD = geometric standard deviation; SD = standard deviation; XR = extended-release

A = Single dose of 2.5 mg saxagliptin (ONGLYZA) and 5 mg dapagliflozin/1000 mg metformin XR (XIGDUO XR) tablets co-administered orally under fed condition;

B = Single dose of triple FCDP consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fed condition;

C = Single dose of triple FCDP tablet consisting of 2.5 mg saxagliptin/5 mg dapagliflozin/1000 mg metformin XR under fasted condition.

For linear scale, vertical lines represent geometric mean ± SD. Samples with actual collection time deviating from nominal collection time by > 10% were excluded from the mean.

Similar rate of absorption (C_{max} and t_{max}) and extent of absorption (AUCs), thus similar bioavailability.

3. *The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.*

- moderate between-subject variability, which was generally similar among treatments, irrespective of the formulations and dietary status; the CV% was 24 to 35% for C_{max} and 27 to 32% for AUCs.

Table 11-13 Summary of Metformin Key Plasma Pharmacokinetic Parameters by Treatment: Cohort 2 (Pharmacokinetic Analysis Set)

Parameter (Unit)		Treatment D (n = 41)	Treatment E (n = 40)	Treatment F (n = 41)
AUC (h*ng/mL)	Geometric Mean	11090 ^a	10470 ^b	9213 ^b
	(CV%)	(31.77)	(30.82)	(26.97)
AUC ₍₀₋₆₎ (h*ng/mL)	Geometric Mean	10910	10420	9248
	(CV%)	(29.72)	(29.79)	(27.63)
C _{max} (ng/mL)	Geometric Mean	1104	1057	1167
	(CV%)	(27.10)	(24.43)	(35.46)
t _{max} (h)	Median	6.00	6.00	4.00
	(Min, Max)	(3.98, 8.10)	(3.00, 8.02)	(2.00, 6.03)
t _{1/2} (h)	Arithmetic Mean	15.15 ^a	15.29 ^b	14.49 ^b
	(SD)	(9.811)	(8.790)	(10.35)

CV% = coefficient of variation (percentage); n: number of subjects in the given category, SD = standard deviation; XR = extended-release

D = Single dose of 5 mg saxagliptin (ONGLYZA®) and 10 mg dapagliflozin/1000 mg metformin XR (XIGDUO® XR) tablet co-administered orally under fed condition;

E = Single dose of triple FCDP consisting of 5 mg saxagliptin/10 mg dapagliflozin/1000 mg metformin XR under fed condition.

F = Single dose of triple FCDP consisting of 5 mg saxagliptin/10 mg dapagliflozin/1000 mg metformin XR under fasted condition.

^a n=38.

^b n=37.

Data Source: Table 14.2.2.2.

4. *The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.*

- The interval of administration once or twice a day and is similar to that of the approved product XIGDUO XR.

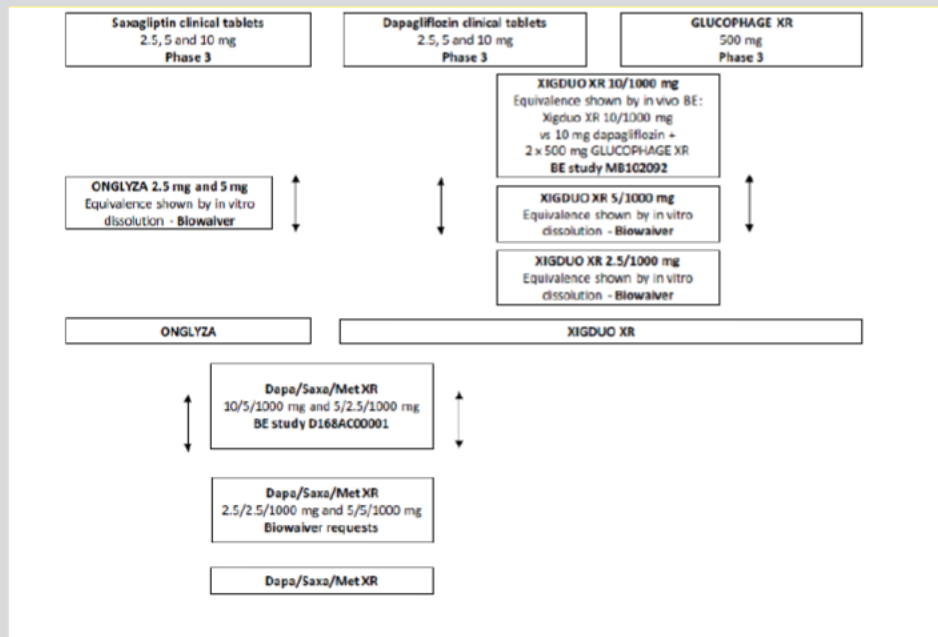
The information submitted adequately supports the extended release designation claim per 21 CFR 320.25(f).

Bridging of Formulations

Reviewer's Assessment: N/A

- The pivotal Phase 3 clinical studies (Studies D1683C00005 and CV181169) used the monocomponents of Dapa/Saxa/Met XR (dapagliflozin, saxagliptin and metformin HCl). The BE study (Study D168AC00001) was designed to bridge the data generated in the 2 pivotal Phase 3 studies to Dapa/Saxa/Met XR tablets.
- The Dapa/Saxa/Met XR mono-components used in phase 3 were bridged to the proposed FCDP tablet Dapa/SaxaMet XR through clinical BE studies and through in vitro dissolution studies.
- Differences between saxagliptin and dapagliflozin clinical presentations in phase 3 and the commercial presentations (Onglyza and Farxiga, respectively) and bridging was done by in vitro dissolution.

- The following Information Request (IR) was communicated to the Applicant on December 11, 2018: You indicated that the differences between saxagliptin and dapagliflozin clinical presentations in phase 3 and the commercial presentations (Onglyza and Farxiga, respectively) were bridged was done by in vitro dissolution, while you have included representative figures, provide the complete individual dissolution profile (individual, mean, SD, profiles) for the products tested.
- The firm submitted individual dissolution profiles for clinical (phase 3) saxagliptin tablets and Onglyza® commercial tablets and individual dissolution profile for clinical (phase 3) dapagliflozin tablets and Farxiga® commercial tablets under supplement S0015 conducted under 3 pH conditions and exhibited similar dissolution profile.
- BE of dapagliflozin, saxagliptin and metformin were established between Dapa/Saxa/Met XR (5/2.5/1000 mg and 10/5/1000 mg) relative to the reference products in healthy subjects when administered in the fed state (Study D168AC00001).



- Batches used in comparative in vitro dissolution studies and in BE study D168AC00001. Dissolution data from the in vitro dissolution tests are graphically presented

<\\cdsesub1\evsprod\nda210874\0001\m2\25-clin-over\clinical-overview.pdf>

Biowaiver Request

Reviewer’s Assessment: Adequate pending acceptable outcome of BE studies and dose proportionality with therapeutic dose range per clinical pharmacology review (please refer to clinical pharmacology review for additional details).

- Dapa/Saxa/Met XR biopharmaceutics program consists of one pivotal BE study and two biowaiver requests.
- The bioequivalence (BE) strategy for the new Dapa/Saxa/Met XR product was a topic of a pre-IND consultation with the Agency (pre-IND meeting request dated August 25, 2016, Seq. 0000; Briefing Package submission dated September 22, 2016, Seq. 0001). As an outcome of this consultation the BE strategy encompassed:

1) A clinical BE study (D168AC00001) performed under standard fed conditions, evaluating two out of four Dapa/Saxa/Met XR tablet strengths (5/2.5/1000mg and 10/5/1000 mg) relative to their individual components (ONGLYZA and XIGDUO XR), and A global registration study (D168AC00001, Table 10) has been conducted to demonstrate bioequivalence (BE) under standard fed conditions between a Dapa/Saxa/Met XR tablet of 5/2.5/1000 mg and a Dapa/Saxa/Met XR tablet of 10/5/1000 mg relative to their individual components (ONGLYZA and XIGDUO XR), co-administered to healthy subjects.

2) Requests for biowaivers for the remaining two Dapa/Saxa/Met XR tablet strengths, 2.5/2.5/1000 mg and 5/5/1000 mg.

- Results from the pivotal BE study (D168AC00001) demonstrating BE for Dapa/Saxa/Met XR 5/2.5/1000 mg and 10/5/1000 mg strengths relative to the co-administered mono component tablets (ONGLYZA and XIGDUO XR) in fed healthy subjects is shown below:

D168AC00001 BE study	BE, PK, food effect, safety	Open label, randomized, 2 parallel cohorts, 3-treatment, 3-period, Crossover	Cohort 1 A. 2.5 mg saxa + 5/1000 mg dapa + met; Fed B. 5/2.5/1000 mg dapa + saxa + met; Fed C. 5/2.5/1000 mg dapa + saxa + met; Fasted Cohort 2 D. 5 mg saxa + 10/1000 mg dapa + met E. 10/5/1000 mg dapa + saxa + met; Fed F. 10/5/1000 mg dapa + saxa + met; Fasted	84/81	Fed and fasted healthy subjects	Single-dose	Complete CSR in Module 5.3.1.2

- Linear clinical PK of dapagliflozin and saxagliptin is observed.
- Physicochemical characteristics of dapagliflozin, saxagliptin and metformin, presenting low biopharmaceutical risk with metformin being classified as a BCS class 3 compounds (high aqueous solubility, low gastrointestinal permeability) and dapagliflozin, and saxagliptin being BCS 1.

- Dapa/Saxa/Met XR of dapagliflozin/saxagliptin/ metformin (Dapa/Saxa/Met XR) 5/2.5/1000 mg and 10/5/1000 mg XR tablets are bioequivalent to the reference products (ONGLYZA and XIGDUO XR) when co-administered under fed-state. Therefore, Food has no apparent effect on the overall systemic exposure (AUC) of dapagliflozin, saxagliptin, 5-hydroxy saxagliptin, and metformin. The C_{max} for dapagliflozin was approximately 38% lower under fed versus fasted-state, but the C_{max} for saxagliptin, 5-hydroxy saxagliptin and metformin were similar between fed and fasted states.
- Acceptable comparative bioequivalence studies on the 5/2.5/1000 mg and 10/5/1000 mg strengths along with similarity in in vitro dissolution performance between products across the physiological pH range support the firm's biowaiver request for the 2.5/2.5/1000 mg and 5/5/1000 mg strengths (please refer to clinical pharmacology review for additional details pertaining to bioequivalence studies and dose proportionality within the therapeutic dose range).

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer Name and Date:

Sarah Ibrahim, Ph.D., August 9, 2018

Sarah Ibrahim, Ph.D., January 17, 2019

Sarah Ibrahim, Ph.D., February 14, 2019

Secondary Reviewer Name and Date:

Haritha Mandula, Ph.D., 12/7/2018, 3/4/2019



Sarah
Ibrahim

Digitally signed by Sarah Ibrahim
Date: 3/12/2019 06:24:07PM
GUID: 546b898a000820c3599fd87d16af9641



Haritha
Mandula

Digitally signed by Haritha Mandula
Date: 3/12/2019 09:46:54PM
GUID: 508da6fb000282df41459408f32a1ce0



Christopher
Galliford

Digitally signed by Christopher Galliford
Date: 3/26/2019 03:40:26PM
GUID: 56324afd003b6374e3a936887dea798c