

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 25-Sep-2014

From: Joseph Leginus, Review Chemist, Branch VII/DNDQA III/ONDQA

To: NDA 205649, XIGDUO™ XR (Dapagliflozin and Metformin HCl Extended Release) Tablet

Subject: CMC Approval Recommendation

Background:

- In Chemistry Review #1 (04-Apr-2014), a recommendation for Approval for NDA 205649 from the standpoint of chemistry, manufacturing and controls was provided pending a) a recommendation of approval from the Biopharmaceutics team, and b) an acceptable cGMP recommendation from the Office of Compliance.
- On 02-Jul-2014, a recommendation for Approval was provided by the Biopharmaceutics Reviewer, T. M. Chen.
- On 24-Sep-2014, Acceptable recommendations were provided for all manufacturing and testing facilities submitted to EES for NDA 205649 and an Overall Compliance recommendation of Acceptable was provided.

Conclusion:

- NDA 205649 is recommended for Approval from the standpoint of chemistry, manufacturing and controls. A recommendation for Approval from Biopharmaceutics has been provided and an overall Office of Compliance recommendation of Acceptable has been provided.

Joseph Leginus, PhD
Review Chemist

Danae Christodoulou, Ph.D.
Branch VII, Chief (Acting), ONDQA

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

/s/

JOSEPH LEGINUS
09/25/2014

DANAE D CHRISTODOULOU
09/25/2014

NDA 205649

XIGDUO™ XR
(Dapagliflozin and Metformin HCl Extended Release)
Tablet

AstraZeneca AB¹

Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #1

¹ On Feb 28, 2014, Bristol-Myers Squibb transferred all rights and ownership, including regulatory responsibility, for NDA 205649 for Dapagliflozin and Metformin Extended Release Tablet to AstraZeneca AB, Sweden.

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
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: in DARRTS.....	12
B. Endorsement Block: in DARRTS.....	12
C. CC Block: in DARRTS.....	12
Chemistry Assessment	13
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	13
S DRUG SUBSTANCES.....	13
P DRUG PRODUCT	20
A APPENDICES	57
R REGIONAL INFORMATION	57
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	59
A. Labeling & Package Insert.....	59
B. Environmental Assessment or Claim of Categorical Exclusion	65

Chemistry Review Data Sheet

1. NDA 205649
2. REVIEW #: 1
3. REVIEW DATE: 04-Apr-2014
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Amendment

Amendment

Document Date

29-Oct-2013

24-Jan-2014

30-Jan-2014

7. NAME & ADDRESS OF APPLICANT:

Name: AstraZeneca AB

Address: Karlebyhus Astraallén, Södertälje, Stockholm County Sweden
SE-151 85

Representative: Amy Jennings, Group Director, Global Regulatory Sciences

Telephone: 203-677-3821

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Xigduo®

b) Non-Proprietary Name (USAN): Dapagliflozin/Metformin Hydrochloride

c) Code Name/# (ONDC only): Dapa/Met XR

d) Chem. Type/Submission Priority (ONDC only):

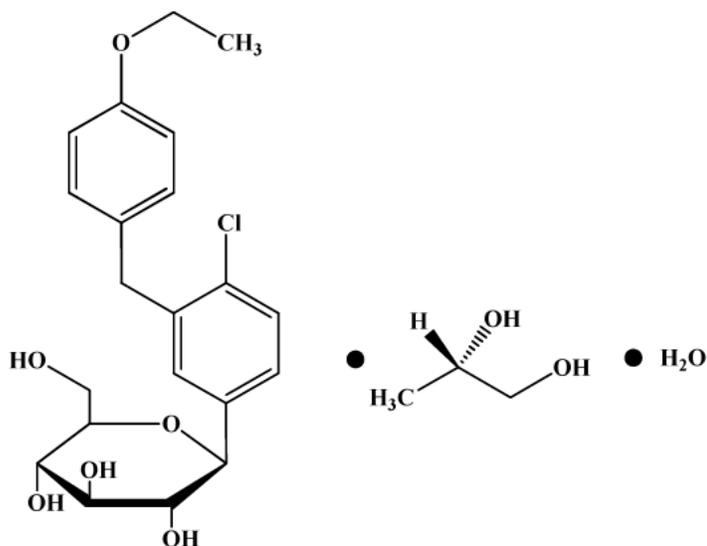
- Chem. Type: 1
- Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.
10. PHARMACOL. CATEGORY: Dapagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2), the major transporter responsible for renal glucose reabsorption; metformin is an antihyperglycemic agent in the biguanide class which acts by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis.
11. DOSAGE FORM: Combination Tablet
12. STRENGTH/POTENCY:
Dapagliflozin/Metformin HCl tablets are manufactured in four strengths (dapagliflozin/metformin HCl): 5 mg/500 mg, 10 mg/500 mg, 5 mg/1000 mg and 10 mg/1000 mg.
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:
- A. Dapagliflozin
Chemical Name (IUPAC): (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro- 2H-pyran-3,4,5-triol, (2S)-propane-1,2-diol (1:1) monohydrate

Chemistry Review Data Sheet

Structural Formula:

Molecular Formula: C₂₁H₂₅ClO₆ • C₃H₈O₂ • H₂O

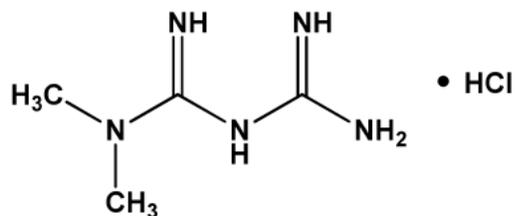
Molecular Weight: 502.98 (1,2-propanediol, monohydrate)

(b) (4)

B. Metformin Hydrochloride

Chemical Name: N,N-Dimethylimidodicarbonimidic diamide hydrochloride

Structural Formula:

Molecular Formula: C₄H₁₁N₅ • HCl

Molecular Weight: 165.6

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	2-Apr-2014	Reviewed by J. Leginus
	II			1	Adequate	2-Apr-2014	Reviewed by J. Leginus
	III			1	Adequate	18-Apr-2011	Reviewed by L. Qi
	III			1	Adequate	22-Nov-2010	Reviewed by P. Jiang
	III			1	Adequate	12-Mar-2009	Reviewed by B. Kurtyka
	III			1	Adequate	8-Jul-2010	Reviewed by C. Strasinger
	III			1	Adequate	20-May-2010	Reviewed by Z. Ying
	III			1	Adequate	24-Oct-2012	Reviewed by D. Klein
	III			1	Adequate	21-Mar-2012	Reviewed by G. Holbert
	III			1	Adequate	11-Mar-2005	Reviewed by G. Holbert

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	202293	Farxiga (dapagliflozin) tablets
NDA	21202	Glucophage XR (metformin hydrochloride) extended release tablets
IND	68652	Dapagliflozin
IND	106890	Dapagliflozin/Metformin FDC

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		
Biopharmaceutics	A request for the Biopharmaceutics evaluation of dissolution data of the drug product has been made. The review is Pending.		
Methods Validation	Not required. No novel methods.		
EA	Categorical Exclusion Requested under 21 CFR §25.31(b).	04-Apr-2014	J. Leginus
Microbiology	Not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth.		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 205649

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 205649 is recommended for Approval from the standpoint of chemistry, manufacturing and controls pending a) a recommendation of approval from the Biopharmaceutics team, and b) an acceptable cGMP recommendation from the Office of Compliance.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

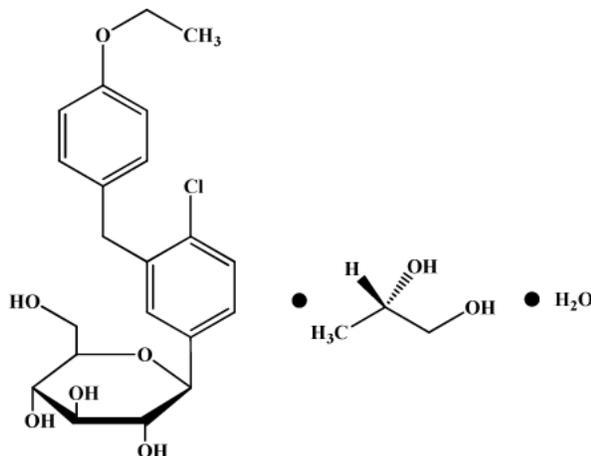
DRUG SUBSTANCES

Dapagliflozin

Dapagliflozin exists as dapagliflozin propanediol monohydrate, (b) (4) a 1:1:1 (b) (4) dapagliflozin, propanediol and water. (b) (4)

The molecular formula of dapagliflozin propanediol monohydrate is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and its molecular weight is 502.98. (b) (4)

Its structural formula is:



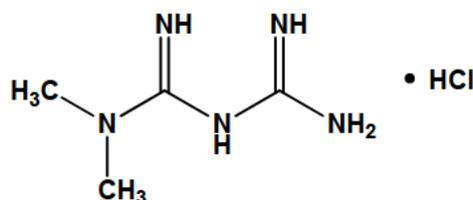
Executive Summary Section

The active component, dapagliflozin, is a potent, highly selective and orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption, leading to urinary glucose excretion.

Information for dapagliflozin drug substance is cross-referenced to the Applicant's² approved NDA 202293 for Farxiga (dapagliflozin) tablets, 5 mg and 10 mg.

Metformin Hydrochloride

Metformin hydrochloride (HCl) is an antihyperglycemic agent in the biguanide class which acts by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. It is a white to off-white crystalline (b) (4) with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin HCl is freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone, ether, and chloroform. The structural formula of metformin HCl is:



Metformin HCl is the active ingredient in the Applicant's previously approved drug product Glucophage® XR (metformin HCl extended-release) tablets. Reference is made to DMF (b) (4) and DMF (b) (4) for information on the chemistry, manufacturing, and controls of metformin HCl. The drug substance is supplied as (b) (4). Copies of the Letters of Authorization to allow the Agency to refer to these DMFs have been provided in the NDA.

DRUG PRODUCT

XIGDUO™ XR is formulated as a fixed dose combination, film-coated (b) (4) biconvex, oval-shaped tablet for oral administration containing immediate-release dapagliflozin and extended-release (XR) metformin HCl drug substances. Four tablet strengths have been developed containing either 5 or 10 mg dapagliflozin and 500 or 1000 mg metformin hydrochloride. The dapagliflozin/metformin HCl XR (Dapa/Met XR) strengths are expressed as dapagliflozin mg (unsolvated, anhydrous) and metformin hydrochloride salt mg as follows:

² On Feb 28, 2014, Bristol-Myers Squibb transferred all rights and ownership, including regulatory responsibility, for NDA 205649 for Dapagliflozin and Metformin Extended Release Tablet to AstraZeneca AB, Sweden.

Executive Summary Section

5 mg/500 mg (Dapa 5/Met XR 500)
5 mg/1000 mg (Dapa 5/Met XR 1000)
10 mg/500 mg (Dapa 10/Met XR 500)
10 mg/1000 mg (Dapa 10/Met XR 1000)

Each strength tablet is uniquely identified by color and numbering debossed on one side and plain on the reverse side.

The manufacturing process is (b) (4)

The four strengths of Dapa/Met XR tablets will be packaged and marketed in a) high density polyethylene (HDPE) bottles with a (b) (4) closure, desiccant, and a heat induction-seal liner (30, 60 or 90 tablets per bottle), or b) HDPE bottle with (b) (4) closure, desiccant, and a heat induction-seal liner (400 or 500 tablets per bottle used for multiple dispensing). Physician samples will be provided in aluminum/aluminum blisters. (b) (4)

Excipients used in the manufacture of Dapa/Met XR tablets (microcrystalline cellulose, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, hypromellose 2208 and 2910) are of compendial grade with the exception of the (b) (4) film coats, however, all components of the film-coat are compendial.

The proposed release specifications include dapagliflozin and metformin HCl identity (HPLC and IR), assay (HPLC), degradates (HPLC), content uniformity and dissolution; appearance, (b) (4) total microbial count and testing for *E. coli*. All non-compendial analytical methods have been validated.

Results from stability studies show that each of the four strengths of the Dapa/Met XR drug product remain stable through 12 months under long-term conditions (30°C/65% RH) and 6 months at accelerated temperature conditions (40°C/75% RH) in both HDPE bottles and aluminum blisters. Also, in-use results show that drug product remains stable when exposed to ambient conditions for up to 12 months which supports use of the multidose 400- and 500-count HDPE bottles. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 24 months is granted for each of the four strengths of Dapa/Met XR tablets when stored at controlled room temperature (20°C to 25°C).

Executive Summary Section

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

The drug product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The goal of the dapagliflozin/metformin HCl combination product was to establish comparable safety and efficacy between the combination tablet and the corresponding individual dapagliflozin and metformin HCl XR tablets when co-administered. The dapagliflozin/metformin HCl XR tablet is intended to provide a more convenient single tablet when a combination of the two drugs is prescribed. Doses are administered once daily with (b) (4). The maximum daily dose is 10 mg for dapagliflozin and 2000 mg for metformin HCl.

C. Basis for Approvability or Not-Approval Recommendation

NDA 205649 is recommended for Approval from the standpoint of chemistry, manufacturing and controls pending a) a recommendation of approval from the Biopharmaceutics team, and b) an acceptable cGMP recommendation from the Office of Compliance.

This is a 505(b)(1) application providing for a new combination oral tablet. Information for dapagliflozin drug substance is cross-referenced to the Bristol-Myers Squibb's² approved NDA 202293 (approved 1/8/2014) for Farxiga (dapagliflozin) tablets, 5 mg and 10 mg. Reference is made to DMF (b) (4) and DMF (b) (4) for CMC information on metformin HCl. Both DMFs have been reviewed (4/2/2014) and found to be adequate. Copies of the Letters of Authorization to allow the Agency to refer to these DMFs have been provided in the NDA.

The dapagliflozin drug substance will be manufactured by (b) (4) located in (b) (4). The metformin HCl drug substance will be manufactured by (b) (4) located in (b) (4). The drug product, XIGDUO® XR (dapagliflozin and metformin HCl extended release) Tablet, will be manufactured by Bristol-Myers Squibb Manufacturing Company located in Humacao, Puerto Rico as a fixed dose combination, film-coated (b) (4) tablet for oral administration containing immediate-release dapagliflozin and extended-release metformin HCl drug substances. All excipients are of compendial grade with the exception of the film coat, however the film coat is manufactured using compendial ingredients. 3 lots of each of the 4 tablet strengths have been manufactured at commercial scale at the proposed site for commercial supply with each lot meeting the specifications proposed. Stability of the drug product has been adequately established in the two container closure systems, HDPE bottles and aluminum blister packs to grant a shelf-life of 24 months when stored at room temperature.

The risk from a safety perspective for this combination drug product is anticipated to be low since each drug substance in dapagliflozin/metformin HCl XR tablet is an active ingredient in two of the Applicant's² previously approved drug products: NDA 202293

Executive Summary Section

for Farxiga (dapagliflozin) tablet and NDA 21202 for Glucophage XR (metformin hydrochloride) extended release tablets.

A recommendation from Biopharmaceutics regarding adequacy of dissolution testing of the drug product is pending.

A recommendation from the Office of Compliance for manufacturing facilities associated with this application is pending.

III. Administrative

- A. Reviewer's Signature:** in DARRTS
- B. Endorsement Block:** in DARRTS
- C. CC Block:** in DARRTS

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

/s/

JOSEPH LEGINUS
04/04/2014

DANAE D CHRISTODOULOU
04/04/2014

I concur with the reviewer's conclusion and recommendation

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205649
2. DATES AND GOALS:

Letter Date: 29-OCT-2013	Submission Received Date : 29-OCT-2013
PDUFA Goal Date: 29-OCT-2014	

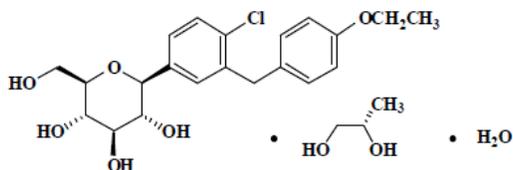
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Proposed: xigduoXR
Established or Non-Proprietary Name (USAN):	Dapagliflozin/metformin hydrochloride
Dosage Form:	Tablet, extended release for the metformin component
Route of Administration	Oral
Strength/Potency	5/500, 5/1000, 10/500, 10/1000 mg/mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of type 2 diabetes
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Dapagliflozin

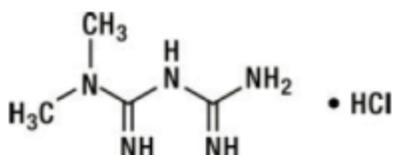
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the formula weight is 502.98. The structural formula is:



**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of C₄H₁₁N₅•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



6. NAME OF APPLICANT (as indicated on Form 356h): Bristol-Myers Squibb

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	1/4
Application Type	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS:
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDQA-PM
Pharmacology/Toxicology		x	
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			Categorical exclusion request to be reviewed by Primary Reviewer
CDRH		x	
Other			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter:
1. The dapagliflozin (b) (4) Provide the location in the NDA of the supporting stability data or amend the application with the data.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes
Biopharmaceutics Comments for 74-Day Letter:
For supporting biowaiver of the two middle strengths (10/500 and 5/1000 mg tablets), the following information is needed. 2. Comparisons of 10/500 mg strength to both of 5/500 (the lowest strength) and 10/1000 mg (the highest strength) i.e., three mean dissolution profiles in the same figure (e.g., Figure 3.1.1A, page 88 under Module 2.7.1) and three mean dissolution data in the same table (e.g., Table 3.1.1A, page 90 under Module 2.7.1) per each dissolution medium (pH1.2, 4.5, and 6.8) per each drug (API) should be reconstructed and submitted. The similarity factor (f ₂) values should be provided if available. 3. Comparisons of 5/1000 mg strength to both of 5/500 (the lowest strength) and 10/1000 mg (the highest strength), i.e., three mean dissolution profiles in the same figure and three mean dissolution data in the same table per each dissolution medium (pH1.0, 4.5, and 6.8) per each drug (API) should be reconstructed and submitted. The similarity factor (f ₂) values should be provided if available.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Microbiology: not applicable

From: [CDER OPS IO MICRO](#)
To: [Tran, Suong T](#); [Christodoulou, Danae D](#); [Ghosh, Tapash](#); [Kumar, Priyanka](#); [CDER OPS IO MICRO](#)
Subject: RE: NEW NDA 205649 dapagliflozin and metformin HCl extended release tablets
Date: Thursday, October 31, 2013 1:16:05 PM

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval. Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

Thanks, Vera

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes
Suggested expertise for team: "small synthetic molecule" drug substance and "extended release solid oral dosage form" drug product	

Summary of Critical Issues and Complexities

Initial Quality Assessment

Previous quality-related meeting between FDA and the sponsor:

IND106,890 Submissions
SN0000 (15-Oct-2009),
SN0017 (29-Jul-2010),
and SN0027 (30-Dec-
2010)

FDA letters dated
7-Jun-2010, 24-Sep-2010,
and 16-Mar-2011

BMS/AZ/FDA agreed that two bioequivalence (BE) evaluations (5 mg dapagliflozin/500 mg metformin XR FDC tablets and 10 mg dapagliflozin /1000 mg metformin XR tablets vs. their respective individual components) will be conducted to support the dapagliflozin/metformin XR FDC. A biowaiver request for two additional strengths (10 mg dapagliflozin/500 mg metformin XR FDC tablets and 5 mg dapagliflozin/1000 mg metformin XR FDC tablets) will be included with the NDA. The biowaiver package should include:

The BE study results on dapagliflozin 5 mg/metformin 500 mg XR and dapagliflozin 10 mg/metformin 1000 mg XR.

The composition of the FDC tablets.

In vitro dissolution comparison profile data and similarity of values using the compendial and three additional media (e.g., 0.1N HCl, and acetate buffer at pH 4.5 and phosphate buffer 6.8) and the same dissolution testing conditions.

The pivotal BE evaluations will be conducted using the to-be-marketed formulation.

As agreed, the Biowaiver package is included with this submission (Module 2.7.1).

The pivotal BE evaluations were conducted using the to-be-marketed formulation.

Drug Substance. (see the copied specifications at the end of this review)

Reference is made to NDA 202293 (dapagliflozin) for all CMC information on the drug substance dapagliflozin propanediol monohydrate. The applicant is the same for both NDAs. Refer to the CMC reviews of NDA 202293 in DARRTS.

Reference is made to DMF (b) (4) and DMF (b) (4) (metformin HCl) for all CMC information on the drug substance metformin HCl. A letter of authorization from the DMF holder is included in the NDA for FDA to access the DMFs (b) (4). Both DMFs were previously reviewed in support of the referenced NDA 21202 for Glucophage XR (metformin HCl extended release) Tablets (same applicant as for this new NDA).

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Drug Product

The film-coated (b) (4) tablets consist of immediate release dapagliflozin and extended release metformin HCl with the strengths of 5/500, 5/1000, 10/500, 10/1000 mg/mg (dapagliflozin/metformin HCl).

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size
10/500 mg	pink, biconvex, capsule-shaped	"1072" and "10/500" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 500
10/1000 mg	yellow to dark yellow, biconvex, oval-shaped	"1073" and "10/1000" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 90 Bottle of 400
5/500 mg	orange, biconvex, capsule-shaped	"1070" and "5/500" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 500
5/1000 mg	pink to dark pink, biconvex, oval-shaped	"1071" and "5/1000" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 60 Bottle of 90 Bottle of 400

Composition. (see the copied composition table at the end of this review) The film coated tablet has (b) (4)

Comparability of the product used in the clinical studies, stability studies, and commercial product. Stability batches include twelve product batches (3 of each strength) manufactured by the commercial process at pilot scale at a development site (BMS New Brunswick NJ) and twelve product batches (3 of each strength) manufactured by the commercial process at commercial scale and commercial site (BMS Humacao, PR). Two of the batches from BMS Humacao, PR, were used in the pivotal BE studies: Batch 1K68153/1L63771 for the 5/500 strength and Batch 1K67984/1L63770 for the 10/1000 strength.

Product manufacture. The manufacturing process is standard for this type of dosage form and is based on the approved processes of the referenced NDAs for dapagliflozin tablets and metformin HCl extended release tablets. It consists of (b) (4)

, but the supporting stability data cannot be located in the NDA (see 74-day comment). Detailed information (including a risk assessment) is provided on the process development and technology transfer from the BMS New Brunswick NJ site to the commercial BMS Humacao, PR site. No design space is proposed. The applicant notes that eight of the twelve pilot-scale batches manufactured at the BMS New Brunswick NJ site had

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

lower dapagliflozin assay values. An investigation found that the (b) (4) had to be readjusted to correct this issue, and subsequent batches manufactured at the commercial site (BMS Humacao, PR) did not have this issue.

Drug product specification. (see the copied specification at the end of this review)

The drug product specification includes attributes standard for this type of dosage form. Limits on degradation products of dapagliflozin and metformin are based on the approved drug product specifications of the referenced NDAs for dapagliflozin tablets and metformin HCl extended release tablets. Based on the lack of degradation in the dapagliflozin component of the product in the long-term stability studies, no degradants testing is included in the release specification but will be included in the stability specification, with limits well within the applicable ICH thresholds for identification and qualification. The one specified dapagliflozin degradant (b) (4) is (b) (4) degradant that has not been found above the reporting threshold of (b) (4) % in long term stability data. The limits on metformin degradants are also within applicable ICH thresholds.

Dissolution. All dissolution-related information and biowaiver issues will be evaluated by the ONDQA Biopharmaceutics team.

Container closure systems. The drug product will be packaged in HDPE bottles for commercial distribution (see the counts per bottle earlier in this review) and aluminum blisters as physician samples. The applicant states that the safety of the product-contact packaging components is shown by compliance to the indirect food additives. Applicable USP testing per <671> and <661> was conducted. Compatibility is shown by stability data supporting both packaging systems. The reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for oral drug products.

Stability. Sufficient stability data are provided in the submission for filing. The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

- For the twelve product batches (3 of each strength) manufactured by the commercial process at pilot scale at a development site (BMS New Brunswick NJ): Stability data are provided for 24 months at 5 °C, 25 °C/60% RH, and 30 °C/75% RH and for 6 months at 40 °C/75% RH. Additional data are provided for the stress studies (open dish, freeze/thaw cycling, and photostability). The eight batches with low dapagliflozin content (see earlier discussion) showed assay results below the proposed acceptance criteria but there was no overall decreasing trend.
- For the twelve product batches (3 of each strength) manufactured by the commercial process at commercial scale and commercial site (BMS Humacao, PR): Stability data are provided for 12 months at 5 °C and 30 °C/75% RH and for 6 months at 40 °C/75% RH. A matrix study design was used (1/3 reduction in testing under the long term conditions). Additional data are provided for the stress studies (open dish, 50 °C, freeze/thaw cycling, and photostability).

Comparability protocol. None proposed.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

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	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i>.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
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.			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

7.	<p>Are drug substance manufacturing sites 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) 	x		
8.	<p>Are drug product manufacturing 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) 	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

	Parameter	Yes	No	Comment
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) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	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?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			Applicant states that there is no design space and no request for flexibility.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			n/a
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H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			4-JUL-2012	
	II			4-JUL-2012	
	III			18-AUG-2011	
	III			13-FEB-2012	
	III			09-FEB-2012	
	III			22-JUN-2012	
	III			13-AUG-2012	
	III			18-SEP-2013	
	III			29-MAY-2012	
	IV			05-SEP-2012	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		The proposed dissolution method: USP Apparatus 1 (Basket) with 100 rpm in pH 6.8 medium, 1000 mL at 37°C
35.	Is the dissolution test part of the DP specifications?	X		The proposed dissolution acceptance criterion: Q= $\frac{(b)}{(4)}$ % at 30 min (b) (4)
36.	Does the application contain the dissolution method development report?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?	X		The four strengths are (b) (4). Two BE studies were conducted for the highest and the lowest strengths. Waiver is requested for the two middle strengths based on comparison of dissolution profile data.
39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?	X		BCS Class 3
41.				
42.	Is there any in vivo BA or BE information in the submission?	X		

See appended electronic signature page

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Appendix 1. Composition of Drug Product

Table 2.3.P.1.T02: Tablet Compositions of Dapagliflozin/Metformin Hydrochloride Extended-Release Film-Coated Tablets

Component	Quality Standard	Function	Quantity per Tablet (Dapa/Met XR mg/mg)			
			5/500	10/ 500	5/1000	10/ 1000
(b) (4)						
Metformin Hydrochloride/	In-house ^b	Active	(b) (4)			
(b) (4)						
Carboxymethylcellulose Sodium	USP	(b) (4)				
(b) (4)	USP, Ph.Eur.					
Hypromellose 2208	USP, Ph.Eur.					
Hypromellose 2910	USP					
Microcrystalline Cellulose	NF, Ph.Eur.					
Silicon Dioxide	NF					
Magnesium Stearate	NF, Ph.Eur.					
(b) (4)						
Dapagliflozin Propanediol ^d	In-house ^e	Active	(b) (4)			
(b) (4)	NF, Ph.Eur.	(b) (4)				
Lactose Anhydrous	NF, Ph.Eur.					
Croscopvidone	NF, Ph.Eur.					
(b) (4)	NF					
(b) (4)	NF, Ph.Eur.					
(b) (4)		(b) (4)				
Film-Coating Layer						
(b) (4)	In-house ^k		(b) (4)			
	In-house ^k					
	In-house ^k					
	In-house ^k					
	USP, Ph.Eur.					
Total Tablet Weight			1367.07	1367.07	1645.13	1645.13

(b) (4) NA = Not Applicable

^a (b) (4) metformin hydrochloride, USP (b) (4)

^b In-house requirements for the (b) (4) are listed as part of an established BMS Testing Standard Specification; all the components of (b) (4) meet applicable compendial requirements.

^d Dapagliflozin propanediol is a (b) (4) containing 1:1:1 ratio of the active moiety (dapagliflozin), (-)-(+)- 1,2-propanediol, and water. The amount of dapagliflozin is theoretically equivalent to (b) (4) of the input dapagliflozin propanediol.

^e In-house requirements for dapagliflozin propanediol are listed as part of an established BMS Testing Standard Specification.

^f The quantity is based on the theoretical assay "as is" of (b) (4) mg of dapagliflozin propanediol is equivalent to 5 mg of dapagliflozin, and (b) (4) mg of dapagliflozin propanediol is equivalent to 10 mg of dapagliflozin. Adjustments will be made based on the actual assay "as is" of the drug substance batch that will be used for drug product manufacture.

^g Microcrystalline cellulose (b) (4)

^h The target amount of total magnesium stearate is (b) (4)

ⁱ (b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Appendix 2. Drug Product Specification

Table 2.3.P.5.T02: Specification for Dapa/Met XR

Test	Method Number	Acceptance Criteria	Method Description
Appearance	6443	Must match product description	Visual
Identification			
Dapagliflozin (HPLC)	95012271	The retention time of the major peak in the sample chromatogram must correspond to that in the standard chromatogram.	High Performance Liquid Chromatography (HPLC) method using UV detection.
Metformin HCl (HPLC)	95012253		
Dapagliflozin (IR:ATR)	95015162	The spectrum of the sample conforms to the reference spectrum.	Infrared (IR) spectrum compared to that of reference material.
Metformin HCl (IR:ATR)	95015162		
Assay (Potency)			
Dapagliflozin % of label	95012271	(b) (4)	High Performance Liquid Chromatography (HPLC) methods using UV detection.
Metformin HCl % of label	95012253	(b) (4)	High Performance Liquid Chromatography (HPLC) methods using UV detection.
Impurities/Degradants			
Dapagliflozin-Related (%)	95012271	Not required for routine release testing. Perform on stability batches only. If tested, (b) (4) If tested, (b) (4) If tested, (b) (4)	High Performance Liquid Chromatography (HPLC) methods using UV detection.
(b) (4)			
Individual Unspecified Impurities Total Impurities			
Metformin HCl-Related (%)	95012253	(b) (4)	High Performance Liquid Chromatography (HPLC) methods using UV detection.
Individual Unspecified Impurities Total Impurities			
Uniformity of Dosage Units			
Dapagliflozin Content Uniformity	356X, 95012271	Must comply with harmonized compendial requirements.	HPLC method using UV detection; harmonized compendia method is applied for both dapagliflozin and metformin HCl content uniformity testing.
Metformin HCl Content Uniformity	356X, 95012253		
Dissolution (% label):			
Dapagliflozin % Dissolved at 30 min	95012246	NLT (b) (4) Q	A common method is used for the dissolution testing of both (immediate-release) dapagliflozin and metformin HCl extended-release components. Instrument: USP Apparatus 1 (baskets) at 100 rpm; Dissolution Media: 1000 ml of pH 6.8 phosphate buffer (50mM).
Metformin HCl % Dissolved at 1 hr	95012246	NLT (b) (4) and NGT (b) (4)	
% Dissolved at 3 hr		NLT (b) (4) and NGT (b) (4)	
% Dissolved at 10 hr		NLT (b) (4) and NGT (b) (4)	
(b) (4)			
Microbial Limits			
Total Aerobic Count	5450A, 250367	(b) (4) CFU/g	Equivalent to USP and Ph. Eur. monographs
Total Molds/Yeasts		CFU/g	
Escherichia Coli		Absent in 1 g	

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Appendix 3. Drug Substance Specification

Dapagliflozin:

Table 2.3.S.4.T01: Dapagliflozin Propanediol Specification and Summary of Batch Data on Dapagliflozin Propanediol Batches Representative of the Commercial Process and Scale (n = 19)

Test	Method Number (Description)	Acceptance Criterion	Range of Results
Appearance:	95002946 (Visual determination)	Powder	(b) (4)
Color:	95002946 (Visual determination)	White to off-white	(b) (4)
Identification:			
IR-ATR	5315A (General IR)	Must be comparable to a reference standard spectrum obtained under the same conditions	The result for all batches was 'complies'.
Raman (Alternative to IR-ATR)	5323A (Raman spectroscopic method)	Must be comparable to a reference standard spectrum obtained under the same conditions	The result for all batches was 'complies'.
HPLC	95011071 (Specific HPLC method using UV detection at 220 nm) 95012242 (Alternative to 95011071, specific HPLC method using UV detection at 220 nm)	The retention time of the major peak in the sample chromatogram must correspond to that in the standard chromatogram	An HPLC method was implemented as a supplemental identity test for the most recent batches of drug substance at the commercial site; the result for all batches was 'complies'.
Assay (%):	95011071 (HPLC) 95012242 (Alternative to 95011071)	(b) (4) % "as is"	(b) (4) %
Propylene Glycol (%):	95009654 (GC) (b) (4)	(b) (4) % (b) (4) % (Record result from in-process control)	(b) (4) % (b) (4) %
Impurities/Degradants:	95011071 (HPLC) 95012242 (HPLC) (Alternative to 95011071)		
(b) (4) %		≤ (b) (4) %	< (b) (4) %
Individual Other (%)		≤ (b) (4) %	< (b) (4) % for each individual impurity other than that specifically listed
Total (%)		≤ (b) (4) %	< (b) (4) %
Residual Solvents:	95009621 (GC)		
(b) (4) %		≤ (b) (4) % (Record result from in-process control)	NE - < (b) (4) %
(b) (4) %		≤ (b) (4) % (Record result from in-process control)	NE - < (b) (4) %
(b) (4) %:	95011445 (GC)	≤ (b) (4) ppm (Test first 10 batches)	< (b) (4) ppm
Particle Size:	95010365 (LLS)	≥ (b) (4) % by volume of particles smaller than (b) (4) microns	(b) (4) %

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

/s/

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12/10/2013

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12/11/2013

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