

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200678Orig1s000**

**CHEMISTRY REVIEW(S)**

NDA 200-678

**kombiglyze™ XR**  
**(saxagliptin and metformin HCl extended-release)**  
**Tablets**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Bristol-Myers Squibb Co.

P.O. Box 4000,  
Princeton, NJ 08543-4000

**Background:** This NDA is submitted as a 505(b)(1) application. The drug product is a new Fixed Dose Combination. The reference drugs are: Onglyza® (saxagliptin) Tablets (NDA 22-350), Glycophage (metformin HCl) tablets (NDA 20-357) and Glycophage XR (metformin HCl) Tablets (NDA 21-202).

**Indication:** The drug product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate.

**Presentation:** The proposed drug product will be packaged in high density polyethylene (HDPE) bottles with a two-piece, child-resistant, continuous-thread closure having an aluminum-foil induction seal (inner seal). Larger bottles (e.g., pharmacy or institutional packages) have a one piece continuous-thread closure with an aluminum-foil induction seal (inner seal). The bottles contain activated carbon/silica gel desiccant packet(s). Physician samples are packaged in (b) (4) blister.

**Establishments Evaluation Report (EER) Status:** Acceptable

<b>Consults:</b>	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	Acceptable
	Microbiology -	Acceptable
	Pharm Toxicology -	N/A

**Original Submission:** December 30, 2009

**Re-submissions:** N/A  
**Post-Approval CMC Agreements:** None at this time.

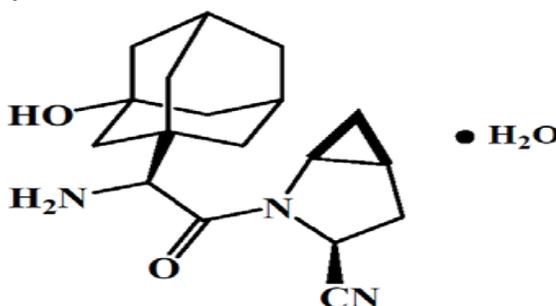
### Drug Substances:

#### Saxagliptin

All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of saxagliptin are provided in NDA 22-350 for Onglyza® (saxagliptin) Tablets (from the same applicant as this NDA). The drug substance saxagliptin will be manufactured at the BMS facility in Sword, Ireland. The retest period for saxagliptin is (b) (4) when stored at USP controlled cold temperature i.e. between 2° and 8°C (36° and 46°F); excursions permitted between 0° and 15°C (32° and 59°F).

#### Structural formula, chemical name, molecular weight and molecular formula

Saxagliptin monohydrate



Chemical Name: (1S,3S,5S)-2-[(2S)-2-Amino-2-(3 hydroxytricyclo [3.3.1.1<sup>3,7</sup>]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.

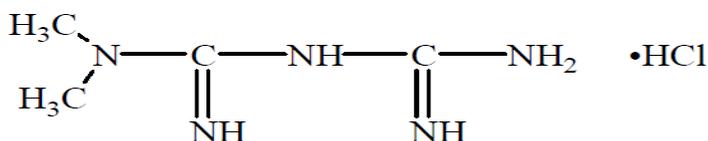
Molecular Weight: 333.43 (315.41 anhydrous) g/mol

Chemical Formula: C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>•H<sub>2</sub>O

#### Metformin HCl

All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of metformin HCl are provided in the Drug Master Files (DMFs) (b) (4) both held by (b) (4). The drug substance is supplied as metformin HCl (b) (4). Both of these DMFs were reviewed and found adequate. The retest period for metformin hydrochloride is (b) (4) when stored in the (b) (4) described in DMF (b) (4) at long term ICH room temperature conditions.

#### Structural formula, chemical name, molecular weight and molecular formula



Chemical name: 1,1- Dimethylbiguanide hydrochloride

Molecular Weight: 165.6 g/mol

Molecular Formula: C<sub>4</sub>H<sub>12</sub>ClN<sub>5</sub>

**Conclusion:** The Drug Substances are adequate.

**Drug Product:**

The proposed drug product is a fixed dose combination of saxagliptin and metformin HCl. The proposed strengths are: saxagliptin 5 mg/metformin HCl 500 mg, saxagliptin 5 mg/metformin HCl 1000 mg, saxagliptin 2.5 mg/metformin HCl 1000 mg. (b) (4)



The application contains a Quality by Design (QbD) approach used during development of the drug product. This approach was utilized for the (b) (4). The QbD implementation approach was similar to the QbD approach used in the approved product ONGLYZA. ONGLYZA was developed following the QbD paradigm and was a part of FDA's CMC Pilot Program. The provided stability data support a shelf life of **15 months** for the blisters and **21 months** for the bottles, when stored at 20° to 25°C (68°-77°F); excursions permitted between 15 and 30°C (59 and 86°F) (see USP Controlled Room Temperature).

**Conclusion:** The Drug Product is adequate.

**Overall Conclusion:** From the CMC point of view, the application is recommended for APPROVAL.

Ali Al-Hakim, Ph.D.  
Branch Chief, Division III  
ONDQA/CDRR/FDA

Container label for the 5 mg/1000 mg presentation



(b) (4)

APPEARS THIS WAY ON  
ORIGINAL

---

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

---

/s/

---

ALI H AL HAKIM  
10/26/2010

**NDA 200-678**

**Tradename™  
(saxagliptin and metformin HCl extended-release)  
Tablets**

**Bristol-Myers Squibb Co.**

**Elsbeth Chikhale, Ph.D.  
ONDQA – Div III – Branch VII  
and  
Sharmista Chatterjee, Ph.D.  
ONDQA – Science and Policy**

**for  
Division of Metabolism and Endocrinology Products**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
I. Recommendations .....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments .....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used .....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block .....	10
<b>Chemistry Assessment .....</b>	<b>11</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Saxagliptin, Swords Laboratories].....	11
S DRUG SUBSTANCE [Metformin HCl, (b) (4)] .....	16
P DRUG PRODUCT [Tradename, Tablet] .....	21
A APPENDICES .....	81
R REGIONAL INFORMATION.....	81
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	82
A. Labeling & Package Insert .....	82
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	82
III. List Of Information Requests Communicated .....	N/A

# Chemistry Review Data Sheet

1. NDA 200-678
2. REVIEW #: 1
3. REVIEW DATE: 30-SEP-2010
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed:	Document Date:
Original	29-DEC-2009
Amendment to original <sup>1</sup>	23-APR-2010
Amendment to original <sup>1</sup>	28-MAY-2010
Amendment to original <sup>2</sup>	03-AUG-2010
Amendment to original <sup>3</sup>	24-SEP-2010

- 1) The 4/23/10 and 5/28/10 amendments provides for updated drug product stability data and a response to the CMC IR dated 3/12/10
- 2) The 8/03/10 amendment provides for a response to the CMC IR dated 7/2/10
- 3) The 9/24/10 amendment provides for a response to the CMC IR dated 9/10/10

7. NAME & ADDRESS OF APPLICANT:

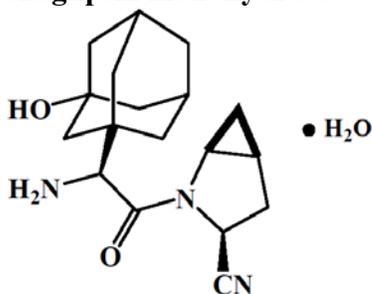
Name:	Bristol-Myers-Squibb Co.
Address:	P.O. Box 4000, Princeton, NJ 08543-4000
Representative:	Pamela J. Smith, M.D., Group Director, GRS
Telephone:	(609) 252-4000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename™
- b) Non-Proprietary Name (USAN): saxagliptin and metformin HCl
- c) Code Name/#:
- d) Chem. Type/Submission Priority:
  - Chem. Type: 4 (new combination)
  - Submission Priority: Standard

## Chemistry Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION:** This NDA is submitted as a 505(b)(1) application. The drug product is a new Fixed Dose Combination (FDC). The reference drugs are: Onglyza® (saxagliptin) Tablets (NDA 22-350), Glycophage (metformin HCl) tablets (NDA 20-357) and Glycophage XR (metformin HCl) Tablets (NDA 21-202).
10. **PHARMACOL. CATEGORY:**  
Saxagliptin is a dipeptidyl peptidase 4 (DPP4) inhibitor.  
Metformin HCl is biguanide antihyperglycemic agent.
11. **DOSAGE FORM:** Tablet
12. **STRENGTH/POTENCY:** 5 mg saxagliptin/ 500 mg metformin HCl  
5 mg saxagliptin/ 1000 mg metformin HCl  
2.5 mg saxagliptin/ 1000 mg metformin HCl
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:**

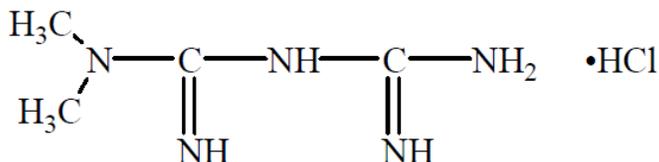
**Saxagliptin monohydrate:**

Chemical name: (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3 hydroxytricyclo [3.3.1.1<sup>3,7</sup>]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate;

Molecular formula: C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>•H<sub>2</sub>O

Molecular weight: 333.43 (315.41 anhydrous) g/mol

## Chemistry Review Data Sheet

**Metformin HCl:**


Chemical name: 1,1-Dimethylbiguanide hydrochloride

 Molecular Formula: Molecular formula: C<sub>4</sub>H<sub>12</sub>ClN<sub>5</sub>

Molecular Weight: 165.6 g/mol

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			3	Adequate	November 13, 2007	Reviewed by Aloka Srinivasan, Ph.D.
	II			1	Adequate	June 29, 2010	Reviewed by Elsbeth Chikhale, Ph.D.

<sup>1</sup> 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 relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other

<sup>2</sup> 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	22-350	Onglyza (saxagliptin) Tablets
NDA	20-357	Glycophage (metformin HCl) Tablets
NDA	21-202	Glycophage XR (metformin HCl) Tablets

Chemistry Review Data Sheet

18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biopharmaceutics	Acceptable	9/27/10	Houda Mahayni, Ph.D.
Biometrics	N/A		
EES	Acceptable	2/9/10	
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	9/30/10	Elsbeth Chikhale, Ph.D.
DMEPA	Pending		
DDMAC	Pending		
EA	Categorical exclusion granted (consult not needed)	9/30/10	Elsbeth Chikhale, Ph.D.
Microbiology	Approval	9/29/10	Jessica Cole, Ph.D.

19. ORDER OF REVIEW: N/A

# The Chemistry Review for NDA 200-678

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for APPROVAL.

The provided stability data support a shelf life of **15 months** for the blisters and **21 months** for the bottles, when stored at 20° to 25°C (68°-77°F); excursions permitted between 15 and 30°C (59 and 86°F) (see USP Controlled Room Temperature). [REDACTED] (b) (4)

Final labeling will be done in coordination with the clinical division.

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

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substances

##### 1) Drug Product

The proposed drug product is a fixed dose combination (FDC) of saxagliptin and metformin HCl. The proposed strengths are: saxagliptin 5 mg/metformin HCl 500 mg, saxagliptin 5 mg/metformin HCl 1000 mg, saxagliptin 2.5 mg/metformin HCl 1000 mg. [REDACTED] (b) (4)

(b) (4)

The total tablet weight is 1180 – 1653 mg. The commercial drug product will be manufactured at the BMS facility in Mount Vernon, IN.

A Quality by Design (QbD) based approach was followed for development of the drug product. This approach was followed only for the (b) (4). The QbD implementation approach was similar to what was followed for another approved product ONGLYZA from BMS, given the similarities between the two products. ONGLYZA was developed following the QbD paradigm and was a part of FDA's CMC Pilot Program.

Following the QbD paradigm, critical quality attributes (CQA) identified for this product were saxagliptin potency and CU (Content Uniformity). The applicant claimed that (b) (4)

(b) (4) However, per the Biopharmaceutics review by Houda Mahayni, Ph.D., dated 9/27/10, this claim is not acceptable because (b) (4)

(b) (4). The applicant has included acceptable dissolution testing as part of the drug product specifications. (b) (4)

Manufacturing control strategy included the following components:

(b) (4)

(b) (4)

The provided stability data do support a shelf life of 21 months when packaged in bottles (b) (4) and the stability data support the proposed shelf life of 15 months (b) (4) in blisters when stored at 20° to 25°C (68°-77°F); excursions permitted between 15° to 30°C (59°-86°F) [see USP Controlled Room Temperature]. The drug product is not sensitive to light exposure. The proposed FDC drug product will be commercialized in high-density polyethylene (HDPE) bottles with a two-piece, child-resistant, continuous-thread closure having an aluminum-foil induction seal (inner seal). Larger bottles (e.g., pharmacy or institutional packages) have a one piece continuous-thread closure with an aluminum-foil induction seal (inner seal). The bottles contain activated carbon/silica gel desiccant packet(s). An additional package for the proposed drug product is a (b) (4) blister (physician samples).

## 2) Drug Substance: Saxagliptin:

The drug substance, saxagliptin, is a previously approved drug substance, produced by (b) (4). All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of saxagliptin are provided in NDA 22-350 for Onglyza® (saxagliptin) Tablets (from the same applicant as this NDA). NDA 22-350 was approved by FDA on 7/31/2009. The drug substance saxagliptin will be manufactured at the BMS facility in Sword, Ireland (same as for NDA 22-350). The retest period for saxagliptin is (b) (4) when stored at USP controlled cold temperature i.e. between 2° and 8°C (36° and 46°F); excursions permitted between 0° and 15°C (32° and 59°F).

## Drug Substance: Metformin HCl:

The drug substance, metformin HCl, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of metformin HCl are provided in the Drug Master Files (DMFs) (b) (4) both held by (b) (4). The drug substance is supplied as metformin HCl (b) (4). DMF (b) (4) was reviewed on 11/13/2007 (review #4 by

Aloka Srinivasan, Ph.D.) and found adequate. DMF (b) (4) was reviewed on 6/29/2010 (review #5 by Elsbeth Chikhale, Ph.D.) and found adequate in support of this NDA. The drug substance metformin HCl will be manufactured by (b) (4). The retest period for metformin hydrochloride is (b) (4) when stored in the (b) (4) described in DMF (b) (4) at long term ICH room temperature conditions.

#### **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 when treatment with both saxagliptin and metformin is appropriate. The maximum daily dose is 5 mg for saxagliptin and 2000 mg for metformin HCl.

#### **C. Basis for Approvability or Not-Approval Recommendation**

From the CMC point of view, the application is recommended for APPROVAL.

The provided stability data support a shelf life of **15 months** for the blisters and **21 months** for the bottles, when stored at 20° to 25°C (68°-77°F); excursions permitted between 15 and 30°C (59 and 86°F) (see USP Controlled Room Temperature). (b) (4)

Final labeling will be done in coordination with the clinical division.

### **III. Administrative**

**A. Reviewer's Signature:** in DARRTS

**B. Endorsement Block:** in DARRTS

**C. cc Block:** in DARRTS

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

---

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

---

/s/

---

ELSBETH G CHIKHALE  
09/30/2010

ALI H AL HAKIM  
09/30/2010

**DATE:** May 10, 2010

**TO:** Saxagliptin/metformin HCl Fixed Dose Combination (FDC) tablets (NDA 200-678) Review Team

**FROM:** Elsbeth Chikhale, Ph.D. ([elsbeth.chikhale@fda.hhs.gov](mailto:elsbeth.chikhale@fda.hhs.gov) 301-796-1659) / Sharmista Chatterjee, Ph.D. (on behalf of the CMC review team)

**THROUGH:** Christine Moore, Ph.D.

**SUBJECT: Consideration for Inspection (CFI) memo**

NDA 200-678 is submitted by Bristol-Myers Squibb Co. (BMS) for (b) (4) (saxagliptin/metformin HCl XR) tablets for oral administration, containing either 5 mg/500 mg, 5 mg/1000 mg or 2.5 mg/1000 mg fixed dose combination (FDC) of saxagliptin/metformin HCl. Both drug substances are active ingredients of previously approved drug products. Saxagliptin is the active ingredient in Onglyza (saxagliptin) Tablets (NDA 22-350), and metformin is the active ingredient in Glycophage (metformin HCl) Tablets (NDA 20-357) and Extended release Glycophage XR (metformin HCl) Tablets (NDA 21-202). The proposed indication is for treatment of patients with type 2 diabetes. The FDC drug product proposed in NDA 200-678 is designed to provide immediate release for saxagliptin and extended release for metformin HCl.

(b) (4)

(b) (4)

(b) (4)

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

The CMC review team is willing to share their knowledge with the investigator prior to and during the inspection. If you have any questions, please email or call the primary CMC reviewer Elsbeth Chikhale, Ph.D. – 301-796-1659; [elsbeth.chikhale@fda.hhs.gov](mailto:elsbeth.chikhale@fda.hhs.gov)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200678	ORIG-1	BRISTOL MYERS SQUIBB	(b) (4) (saxagliptin + metformin XR) Tablets

---

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

---

/s/

---

ELSBETH G CHIKHALE  
05/24/2010

ALI H AL HAKIM  
05/25/2010

Initial Quality/CMC Assessment  
ONDQA

**Division of Metabolism and Endocrinology Products**

**NDA:** 200678

**Applicant:** Bristol-Myers Squibb Co.

**Stamp Date:** 29-DEC-2009

**PDUFA Date:** 29-OCT-2010

**Proposed Proprietary Name:** [none]

**Established Name:** Saxagliptin/metformin hydrochloride

**Dosage form and strength:** Tablet: immediate release saxagliptin and extended  
release metformin hydrochloride –  
5/500, 5/1000, 2.5/1000  
(mg/mg saxagliptin anhydrous free base/  
metformin hydrochloride)

**Route of Administration:** oral

**Indications:** Type 2 diabetes

**CMC Lead:** Su (Suong) Tran, Branch II/DPA I/ONDQA

**ONDQA Fileability:** Yes

Initial Quality/CMC Assessment  
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Review Staff will review the biowaiver requests. Consult request was sent on 25-JAN-2010.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	Compliance: "Acceptable" on 09-FEB-2010
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	The proposed limit of <span style="background-color: #cccccc;">(b) (4)</span> microbial limits will be reviewed by the Microbiology team.
Pharm/Tox	<i>May Not Be Applicable. Proposed limits on impurities are within applicable ICH qualification thresholds.</i>

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 76500.

Reference is made to the DMF (b) (4)

approved NDA 20357, and approved NDA 21202 for all CMC information on the metformin HCl drug substance. This new NDA and the referenced NDAs have the **same applicant**: access to the CMC information in the referenced NDAs and their CMC reviews is permitted.

Reference is made to the approved NDA 22-350 (saxagliptin) for all CMC information on the saxagliptin drug substance. This new NDA and the referenced NDA have the **same applicant**: access to the CMC information in the referenced NDA and its CMC reviews is permitted.

The product is a fixed dose combination tablet available in the strength of 5/500, 5/1000, 2.5/1000 (mg/mg saxagliptin anhydrous free base/metformin hydrochloride). The excipients are carboxymethylcellulose sodium, hypromellose 2208, magnesium stearate, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, and iron oxides. The 5/500 strength also has microcrystalline cellulose and hypromellose 2910. The tablet consists of the extended release metformin

(b) (4) The product will be packaged in HDPE bottles with child-resistant closures and desiccant for commercial distribution, and blister packs as physician samples.

Reference is also made to the approved NDA 22350 (saxagliptin), approved NDA 20357 (metformin HCl) and approved NDA 21202 (metformin HCl) for supporting CMC information on the drug product manufacturing and testing. This new NDA and the referenced NDAs have the same applicant.

**Maximum daily dose is 5 mg saxagliptin and 2000 mg metformin HCl.**

## Initial Quality/CMC Assessment ONDQA

### **Has all information requested during the IND phases, and at the pre-NDA meetings been included?**

The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question.

The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.)

Major CMC issues discussed in the FDA letter dated 17-NOV-2009 include:

- Agreement on the registration stability protocol
- Omission of polymorph testing in the drug product specification

Major issues discussed in the FDA letter dated 20-MAR-2009 include:

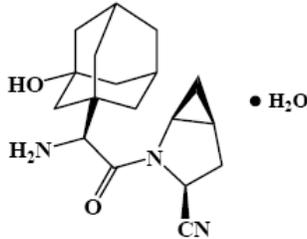
(b) (4)

Initial Quality/CMC Assessment  
ONDQA

**Drug substance:**

**Saxagliptin monohydrate:**

Chemical Name (CAS): (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo-[3.3.1.1<sup>3,7</sup>]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate



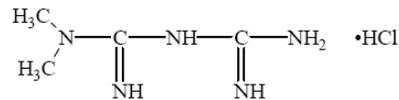
Molecular Formula: C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> • H<sub>2</sub>O

Formula Weight: 333.43 (315.41 anhydrous)

**Metformin hydrochloride:**

1,1-Dimethylbiguanide hydrochloride

*N,N*-Dimethylimidodicarbonimidic diamide hydrochloride



**3.2.S.1.2.2 Molecular formula**

C<sub>4</sub>H<sub>12</sub>ClN<sub>5</sub>

**3.2.S.1.2.3 Molecular weight**

MW = 165.6

**Review comments:**

- Reference is made to the DMF [REDACTED] (b) (4) [REDACTED], approved NDA 20357, and approved NDA 21202 for all CMC information on the metformin HCl drug substance. No issue should be found for metformin HCl because only the

## Initial Quality/CMC Assessment ONDQA

approved information in NDA 20357 and NDA 21202, including the information in their supporting DMFs [REDACTED] <sup>(b) (4)</sup>, will be referenced.

- Reference is made to the approved NDA 22-350 (saxagliptin monohydrate) for all CMC information on the saxagliptin drug substance. This new NDA and the referenced NDA have the same applicant. No issue should be found for saxagliptin because only the approved information in NDA 22350 will be referenced.
- The drug substance specifications are included in the NDA. The applicant states that the metformin HCl specification is the same as the approved specification in the referenced NDA 20357. No such statement is given for the saxagliptin specification, and the reviewer will confirm that this specification is the same as the approved on in the referenced NDA 22350.

Initial Quality/CMC Assessment  
ONDQA

**Drug product**

The composition of the drug product is copied the following pages.



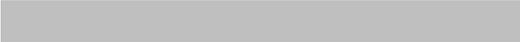
**Review comments:**

- **Established name and dosage strength.** The proposed established names of the product are “saxagliptin” and “metformin hydrochloride”, which are acceptable because they correlate with the dosage strengths as per current CDER policy on nomenclature. The dosage strength of saxagliptin is of the anhydrous free base. As discussed in the reviews of the referenced approved NDA 22350, the drug substance saxagliptin monohydrate  (b) (4) . The reviewer will ensure that the full amount of the saxagliptin hydrochloride salt is included in the prescribing information and packaging labels, but it should not have the same prominence as the dosage strength.
- **Dosage form.** The product is a fixed dose combination tablet available in the strength of 5/500, 5/1000, 2.5/1000 (mg/mg saxagliptin anhydrous free base/metformin hydrochloride). Each tablet consists of  (b) (4)



Initial Quality/CMC Assessment  
ONDQA

(b) (4)

- **Quality control of excipients.** (b) (4) is a degradant (b) (4)  
  
  

- **Comparability of the product used in the clinical studies, stability studies, and commercial product.**
  - 5/500 dosage strength: Product batch 7L24093 was used in the pivotal study CV181060 to show BE between the 5/500 tablet to the co-administered 5 mg saxagliptin and 500 mg metformin HCl approved products. The only formulation difference between batch 7L24093 and the commercial product is in the color and print. This batch had a yellow coat vs. the commercial butterscotch color coat, and this batch did not have any code printing. The color and printing difference should not affect the performance of the product. Primary stability batches have the same formulation as the commercial product, as confirmed by the applicant in the 25-JAN-2010 amendment.
  - 5/1000 dosage strength: Product batch 8E43429/8C4324Z was used in the pivotal study CV181076 to show BE between the 5/1000 tablet to the co-administered 5 mg saxagliptin and 1000 mg metformin HCl products. The only formulation difference between batch 8E43429/8C4324Z and the commercial product is in the print. This batch did not have any code printing. The printing difference should not affect the performance of the product. Primary stability batches have the same formulation as the commercial product, as confirmed by the applicant in the 25-JAN-2010 amendment.

Initial Quality/CMC Assessment  
ONDQA

**CHEMISTRY NDA FILEABILITY CHECKLIST**

**IS THE CMC SECTION OF APPLICATION FILEABLE? YES**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	x		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		Exclusion request per 21 CFR 25.31 is included.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		By reference to DMFs.
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?	x		Requested information may be in different locations in NDA.
8	Have draft container labels and package insert been provided?	x		
9	Have all DMF References been identified?	x		
10	Is information on the investigational formulations included?	x		
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?			Not applicable.

(b) (4)

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200678

-----  
ORIG-1

-----  
BRISTOL MYERS  
SQUIBB

-----  
 (b) (4) (saxagliptin +  
metformin XR) Tablets

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

/s/  
-----

SUONG T TRAN  
02/17/2010

PRASAD PERI  
02/17/2010  
I concur