APPLICATION NUMBER:
200678Orig1s000

CHEMISTRY REVIEW(S)
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 blister.

Establishments Evaluation Report (EER) Status: Acceptable

Consults: 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 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

![Structural formula of saxagliptin monohydrate]

Chemical Name: \((1S,3S,5S)-2-[(2S)-2-Amino-2-(3 hydroxytricyclo [3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.\)
Molecular Weight: 333.43 (315.41 anhydrous) g/mol
Chemical Formula: \(C_{18}H_{25}N_{3}O_{2}\cdot H_{2}O\)

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) both held by The drug substance is supplied as metformin HCl. Both of these DMFs were reviewed and found adequate. The retest period for metformin hydrochloride is when stored in the described in DMF at long term ICH room temperature conditions.

Structural formula, chemical name, molecular weight and molecular formula

![Structural formula of metformin HCl]
Chemical name: 1,1- Dimethylbiguanide hydrochloride  
Molecular Weight: 165.6 g/mol  
Molecular Formula: C₄H₁₂ClN₅  

**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.

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
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

Table of Contents .......................................................................................................................... 2

Chemistry Review Data Sheet........................................................................................................ 3

The Executive Summary .................................................................................................................. 7

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

Chemistry Assessment ................................................................................................................... 11

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:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>29-DEC-2009</td>
</tr>
<tr>
<td>Amendment to original^1</td>
<td>23-APR-2010</td>
</tr>
<tr>
<td>Amendment to original^1</td>
<td>28-MAY-2010</td>
</tr>
<tr>
<td>Amendment to original^2</td>
<td>03-AUG-2010</td>
</tr>
<tr>
<td>Amendment to original^3</td>
<td>24-SEP-2010</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Bristol-Myers-Squibb Co.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>P.O. Box 4000, Princeton, NJ 08543-4000</td>
</tr>
<tr>
<td>Representative:</td>
<td>Pamela J. Smith, M.D., Group Director, GRS</td>
</tr>
<tr>
<td>Telephone:</td>
<td>(609) 252-4000</td>
</tr>
</tbody>
</table>

8. DRUG PRODUCT NAME/CODE/TYPg:
   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
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 a 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: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
- _x_Spots product __Form Completed
- __Not a SPOTS product

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

Saxagliptin monohydrate:

![Chemical Structure]

Chemical name: (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetil]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate;
Molecular formula: C_{18}H_{25}N_{3}O_{2}•H_{2}O
Molecular weight: 333.43 (315.41 anhydrous) g/mol
Chemistry Review Data Sheet

Metformin HCl:

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{C} \quad \text{NH} \quad \text{C} \quad \text{NH}_2 \quad \cdot \text{HCl}
\]

Chemical name: 1,1-Dimethylbiguanide hydrochloride
Molecular Formula: Molecular formula: C$_4$H$_{12}$ClN$_5$
Molecular Weight: 165.6 g/mol

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE$^1$</th>
<th>STATUS$^2$</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>Adequate</td>
<td>November 13, 2007</td>
<td>Reviewed by Alok Srinivasan, Ph.D.</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Adequate</td>
<td>June 29, 2010</td>
<td>Reviewed by Elsbeth Chikhale, Ph.D.</td>
</tr>
</tbody>
</table>

$^1$ 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 relevant revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other

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

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>22-350</td>
<td>Onglyza (saxagliptin) Tablets</td>
</tr>
<tr>
<td>NDA</td>
<td>20-357</td>
<td>Glycophage (metformin HCl) Tablets</td>
</tr>
<tr>
<td>NDA</td>
<td>21-202</td>
<td>Glycophage XR (metformin HCl) Tablets</td>
</tr>
</tbody>
</table>
18. STATUS:

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

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).

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.
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 [specific component or process]. 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 [claim or statement about CQA]. However, per the Biopharmaceutics review by Houda Mahayni, Ph.D., dated 9/27/10, this claim is not acceptable because [reason or evidence]. The applicant has included acceptable dissolution testing as part of the drug product specifications.

Manufacturing control strategy included the following components:
The provided stability data do support a shelf life of 21 months when packaged in bottles and the stability data support the proposed shelf life of 15 months 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 blister (physician samples).

2) Drug Substance: Saxagliptin:

The drug substance, saxagliptin, is a previously approved drug substance, produced by . 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 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) both held by . The drug substance is supplied as metformin HCl . DMF was reviewed on 11/13/2007 (review #4 by
Aloka Srinivasan, Ph.D.) and found adequate. DMF 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 . The retest period for metformin hydrochloride is when stored in the described in DMF 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°C to 25°C (68°F-77°F); excursions permitted between 15 and 30°C (59 and 86°F) (see USP Controlled Room Temperature).

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
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 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 (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.
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
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-200678</td>
<td>ORIG-1</td>
<td>BRISTOL MYERS SQUIBBB</td>
<td>(saxagliptin + metformin XR) Tablets</td>
</tr>
</tbody>
</table>

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
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
<table>
<thead>
<tr>
<th>CONSULTS/ CMC RELATED REVIEWS</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopharmaceutics</td>
<td>The ONDQA Biopharmaceutics Review Staff will review the biowaiver requests. Consult request was sent on 25-JAN-2010.</td>
</tr>
<tr>
<td>CDRH or CBER</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>EA</td>
<td>The categorical exclusion claim will be assessed by Primary Reviewer.</td>
</tr>
<tr>
<td>EES</td>
<td>Compliance: “Acceptable” on 09-FEB-2010</td>
</tr>
<tr>
<td>OSE</td>
<td>Labeling consult request will be sent as part of DMEP’s request.</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Validation may be requested of FDA labs after test methods are finalized.</td>
</tr>
<tr>
<td>Microbiology</td>
<td>The proposed limit of microbial limits will be reviewed by the Microbiology team.</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>May Not Be Applicable. Proposed limits on impurities are within applicable ICH qualification thresholds.</td>
</tr>
</tbody>
</table>

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

Reference is made to the DMF 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 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.
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:
  o Agreement on the registration stability protocol
  o Omission of polymorph testing in the drug product specification

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

(b) (4)
Drug substance:

Saxagliptin monohydrate:

Chemical Name (CAS): \((15S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo-[3.3.1.3^7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate\)

Molecular Formula: \(C_{18}H_{25}N_{3}O_{2} \cdot H_{2}O\)

Formula Weight: 333.43 (315.41 anhydrous)

Metformin hydrochloride:

1,1-Dimethylbiguanide hydrochloride

\(N,N\)-Dimethylimidodicarbonimidic diamide hydrochloride

\(C_2H_12ClN_5\)

3.2.1.2.3 Molecular weight

\(MW = 165.6\)

Review comments:

- Reference is made to the DMF, 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
approved information in NDA 20357 and NDA 21202, including the information in their supporting DMFs, 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.
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. 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...
• **Quality control of excipients.** is a degradant

• **Comparability of the product used in the clinical studies, stability studies, and commercial product.**
  
  o **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.

  o **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.
**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.

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

15 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-200678</td>
<td>ORIG-1</td>
<td>BRISTOL MYERS</td>
<td>(saxagliptin + metformin XR) Tablets</td>
</tr>
</tbody>
</table>

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